AN EVALUATION OF INTERMITTENTLY INFLATED EXTREMITY CUFFS IN PREVENTING THE CARDIOVASCULAR DECONDITIONING OF BEDREST AND WATER IMMERSION

by

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FOREWORD

This report presents the results of an evaluation of the effectiveness of intermittently inflated extremity cuffs and leotards in preventing or controlling the cardiovascular deconditioning associated with bedrest and water immersion. In the Appendix, there are presented complete technical reports on different phases of the work that has been performed at the Texas Institute for Rehabilitation and Research, including preliminary studies conducted under an earlier contract. The information on earlier studies has been included to provide comprehensive documentation of the work that has been performed in this research laboratory. The presentation of the data, discussion, and suggested interpretations are the responsibility of the author and do not represent the views of the National Aeronautics and Space Administration.

This contract, NAS 9-5821, was initiated from the National Aeronautics and Space Administration. Technical direction has come from Dr. Lawrence F. Dietlein, Mr. William V. Judy, and Mr. Carter Alexander. Dr. Robert L. Jones participated in a feasibility study designed to determine specifications for updating a data acquisition, display, storage, and a retrieval system for the Crew Systems Division pressure chamber. Computer services were provided free of charge at the Texas Medical Center, Regional Computer Facility, under sponsorship of NIH Grant FR 00254.

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INTRODUCTION

On Project Mercury flights MA-8 and MA-9, cardiovascular orthostatic instability and body weight changes were observed which possibly could reflect changes in blood volume, venomotor tone, or other cardiovascular reflex mechanisms. The use of intermittently inflated tourniquets on the extremities in total body water immersion studies conducted by Graveline indicated maintenance of cardiovascular adaptability. Such a potential technique for the maintenance of cardiovascular adaptability was thought to be ideal for application to the space flight situation because of the small size of the components of the system, the ability of the technique to act in the zero gravity situation, and because of minimum interference with astronaut participation in activities of space flight.

Although the physiological mechanisms accounting for the apparent cardiovascular protection in earlier studies is obscure, several hypotheses have been proposed. It is thought by some investigators that intermittent obstruction of the venous return causes peripheral venous pressure to increase, resulting in pooling of blood in the extremities, thus temporarily decreasing venous return to the heart. Such changes potentially could prevent a continuous thoracic blood volume overload, thus inhibiting the Henry-Gauer reflex, with the resulting diuresis leading to an ultimate decrease in the circulating blood volume (plasma volume). It also was thought that the use of the cuff technique would produce pressure variations in the venous system which would simulate the hydrostatic pressure effects found when the long axis of the body is exposed to the gravity vector, thus helping the cardiovascular system retain its capacity to adjust to positional changes, either through maintenance of venomotor tone or by preventing the transfer of fluid out of the extravascular space.

At the time of planning for inclusion of extremity cuffs as a cardiovascular reflex conditioning experiment on Gemini flights, only water immersion experiments had been conducted to demonstrate the apparent protective effect derived from the use of this technique. Since that time, other experimental studies to produce deconditioning have been conducted utilizing water immersion and bedrest to test the effectiveness of different extremity cuff configurations and timing cycles. The results of the studies conducted in association with this contract are reported in the Appendix of this report. Since the primary purpose of the cardiovascular reflex conditioning experiment was to prevent orthostatic cardiovascular instability, the tilt table test was selected as the most meaningful test to help assess the effectiveness of the use of cuffs.

Tilt table tests were performed before and after each of the deconditioning experiments. In addition, plasma volume determinations were performed since changes could effect tilt table intolerance.

DISCUSSION

The results of the many studies conducted by the author cannot be presented conveniently in a single report because of differences in experimental design and differences in responses for each group of subjects. Therefore, this discussion will be limited only to a summary of the findings for each of the experimental studies. The pertinent literature review, results, and evaluations of each of the experiments conducted are discussed in the separate reports presented in the Appendix. A more detailed presentation of the use of extremity cuffs as a cardiovascular reflex conditioning technique is presented in the final report for Contract NSR 44-024-006, March, 1967, presented to the National Aeronautics and Space Administration Headquarters.

The initial studies performed at the Texas Institute for Rehabilitation and Research were designed to reproduce the earlier findings of Graveline, who demonstrated a protective effect from the use of intermittently inflated extremity cuffs in water immersion experiments. The technical reports describing these studies are contained in Appendix F and Appendix G of this document. Tilt table intolerance on four healthy young adult males was studied in two water immersion experiments of 6 hours duration. Body weight, fluid intake, urine output, and leg circumference measurements were made and recorded. After the first period of 6 hours water immersion, three of the four subjects experienced syncope during a tilt table test. Compared to pre-immersion tilt tests, all subjects experienced marked changes in heart rate and blood pressure during tilt table tests after water immersion. A significant diuresis was not noted. During the second period of immersion, cuff-tourniquets were applied to the four extremities and inflated to a pressure of 60 mm. Hg, with an inflation-deflation cycle of 1-minute-on, 1-minute-off. Some degree of protection against tilt table intolerance after immersion was observed in this experiment; none of the subjects experienced syncope or showed the marked blood pressure changes they had shown on the previous immersion test without extremity cuffs. In these same experiments, repeated plasma volume, hemoglobin, hematocrit, and serum sodium, potassium, osmolarity, and protein determinations were performed. An increased rate of transfer of intravascular protein, as well as fluid and electrolytes, into the extravascular compartment was suggested as one of the possible factors responsible for the manifestations observed during the tilt table tests after the water immersion. The results of this study were interpreted as confirmation of the previous findings of Graveline.

The next experiment was conducted to evaluate the effectiveness of lower extremity cuffs in the bedrest situation. Eleven healthy adult male subjects were studied using tilt table procedures before and after three 10 day periods of recumbency. Cuffs on the lower extremities were inflated intermittently on each of the subjects during one of the periods of recumbency. Definite cardiovascular deconditioning, as manifested in statistically significant changes in the tilt table response, was observed after each recumbency period. No statistical difference was observed in comparing the tilt table response for the recumbency periods in which the potential treatment was added or omitted. The lack of protection in the bedrest situation could be attributed to different mechanisms of deconditioning, to the use of extremity cuffs on only the lower extremities, to the use of a different inflation-deflation timing cycle (5-minutes-on, 10-minutes-off), or to the relatively narrow cuffs used. The detailed results of this study are contained in Appendix D of this report.

The plasma volume and extracellular fluid volume changes associating the same 10 day bedrest studies described above are documented in Appendix E. A significant decrease in plasma volume occurred during the first several days of recumbency; fluid volume decrease was progressive over the recumbency period. The use of intermittent inflation of cuffs on the lower extremities did not influence the plasma volume and extracellular fluid volume change seen in association with 10 days bed recumbency. Because of the continued suggested protection from use of the intermittently inflated extremity cuffs in the water immersion condition, but no protection from the bedrest situation, more complex experimental studies were performed.

The tilt table response of nine experimental subjects was evaluated before and after short term periods of deconditioning, including chair rest, bedrest, water immersion, and water immersion with cuffs. The deconditioning experiments were conducted using the following eight experimental conditions: (a) water immersion; (b) water immersion, arm cuffs only; (c) water immersion, leg cuffs only; (d) water immersion, arm and leg cuffs; (e) bedrest; (f) chair rest; (g) water immersion with leg cuffs, last 4 hours; and (h) water immersion with leg cuffs, 15 minutes per hour. In water immersion experiments, the subjects were immersed in a sitting position, head-out, with a water temperature of 94°F. Cuffs were inflated to 70 mm. Hg for 2 of every 6 minutes. The results of this study indicate that a definite cardiovascular deconditioning occurred with water immersion, as evidenced in the plasma volume decline and the tilt table response. There was a significant decline in plasma volume during all experimental conditions except chair rest. No definite protective effect was observed from the use of intermittently inflated extremity cuffs. There was, however, some suggested protective effect from the use of the intermittently inflated extremity cuffs on the upper extremities.

A later experiment, as reported in Appendix A, was designed to evaluate the plasma volume and tilt table response to water immersion deconditioning experiments using extremity cuffs. The plasma volume and tilt table response of six healthy adult male subjects was evaluated before and after six periods of water immersion deconditioning; the immersion periods were of 12 hours duration. A Latin Square experimental design was utilized employing six different treatments: (a) water immersion, no cuffs; (b) water immersion, no cuffs; (c) water immersion with arm cuffs, 1-minute-on, 1-minute-off; (d) water immersion with arm cuffs, 2-minutes-on, 4-minutes-off; (e) water immersion with arm cuffs, 5-minutes-on, 10-minutes-off; and (f) water immersion with leg cuffs, 5-minutes-on, 10-minutes-off. Cuffs were inflated to an effective pressure of 60-70 mm. Hg. The subjects were immersed in a sitting position, head-out, with the water temperature maintained at 93°F. The results of the study indicate that cardiovascular deconditioning occurred during immersion as evidenced by a decline in plasma volume and tilt table manifestations of orthostatic intolerance. There was no statistically significant difference in the tilt table response or plasma volume change for any of the experimental treatment conditions. For this group of subjects, under well controlled experimental conditions, no significant protective effect was found with the use of extremity cuffs. The mechanism for the apparent protection afforded by cuffs in other experiments and not in this study was not evident.

Since the earlier water immersion studies showed only a suggested protective effect which was not confirmed by later more extensive studies, and because the effectiveness of extremity cuffs in bedrest situations was questionable, a final experiment was designed to evaluate further the use of extremity cuffs in the bedrest situation. This study is reported in Appendix C. In addition, the use of leotard garments was evaluated as a means to protect against the manifestations of cardiovascular deconditioning of bedrest. Six healthy young adult male subjects were studied during three 14 day periods of bedrest with the experimental conditions of bedrest, bedrest with arm cuffs, and bedrest with arm cuffs and leg cuffs. The inflation-deflation cycle for the extremity cuffs was 2-minutes-on, 4-minutes-off, with an inflation pressure of 70 mm. Hg. Tilt table and plasma volume studies were performed on subjects before and after each 14 day period of deconditioning. The tilt procedure consisted of two consecutive tilts performed on each subject before and after bedrest, with the subject wearing leotards for the first tilt, followed by a tilt without the use of leotards. The use of extremity cuffs was confined to the period of deconditioning only. These studies indicated that after deconditioning has occurred, leotards on the subjects provided a protective effect against the tilt table manifestations of cardiovascular deconditioning. There is a suggested protective effect, though not statistically significant, from the use of intermittently inflated upper extremity cuffs during recumbency.

CONCLUSIONS

1. No significant protection against cardiovascular deconditioning associated with bedrest or water immersion experiments could be attributed to the use of intermittently inflated extremity cuffs.

2. The use of pressure garments on the lower extremities provides a statistically significant protective effect against the manifestations of cardiovascular deconditioning resulting from bedrest or water immersion.

APPENDIX

PLASMA VOLUME AND TILT TABLE RESPONSE TO WATER IMMERSION DECONDITIONING EXPERIMENTS USING EXTREMITY CUFFS

by

Fred B. Vogt, M.D.

INTRODUCTION

Graveline,[1] in 1963, showed a protective effect against the tilt table intolerance seen after water immersion by the use of extremity cuffs intermittently inflated using a 1-minute-on, 1-minute-off inflation-deflation cycle. Vogt,[4,5] in bedrest studies conducted in 1964, did not demonstrate a protective effect of lower extremity cuffs intermittently inflated using a 5-minute-on, 10-minute-off inflation-deflation cycle. Vogt[2] did confirm in water immersion studies a protective effect from cuffs with an inflation-deflation cycle of 1-minute-on, 1-minute-off; and, because of the experimental design, interpreted the results as being due primarily to the cuffs inflated on the upper extremity. Vogt and Johnson[3] found an increased rate of disappearance of tagged albumin from the vascular system and a decline in plasma volume during immersion, and suggested this as one possible contributing mechanism for the cardiovascular deconditioning seen with water immersion. The use of the extremity cuffs reduced the rate of disappearance of the tagged albumin, decreased the loss of plasma volume, and provided an apparent protection against the tilt table intolerance.

It was the purpose of the experiment reported herein to study further the mechanism of the protective effect seen with the use of intermittently inflated extremity cuffs by comparing different cuff configuration and inflation times on the same group of subjects who underwent repeated water immersion experiments.

From the Texas Institute for Rehabilitation and Research, Houston, Texas. This research was conducted under sponsorship of the National Aeronautics and Space Administration, under Contract NAS 9-5821. Computer services were provided at the Texas Medical Center, Regional Computer Facility, under sponsorship of NIH Grant FR 00254.

Dr. Vogt is associated with the Texas Institute for Rehabilitation and Research, Houston, Texas; and The University of Texas Graduate School of Biomedical Sciences, Houston, Texas.

METHOD

Subjects

Six healthy adult male subjects participated in this study involving six experimental conditions. For each subject, a complete medical history was compiled, and a physical examination (with appropriate laboratory tests) was performed to exclude subjects with any conditions contraindicatory to their participation in the study. Subject characteristics are presented in Table I.

Experimental Design

In Table II is shown the experimental design in which the subjects participated. The duration of each of these experimental conditions was 12 hours. A Latin Square experimental design was used to assign the six treatments of (a) water immersion, no cuffs, (b) water immersion, no cuffs, (c) water immersion, arm cuffs, 1-minute-on, 1-minute-off, (d) water immersion, arm cuffs, 2-minutes-on, 4-minutes-off, (e) water immersion, arm cuffs, 5-minutes-on, 10-minutes-off, and (f) water immersion, leg cuffs, 5-minutes-on, 10-minutes-off. The subjects underwent water immersion studies on Monday and Thursday for three successive weeks.

Experimental Protocol

The subjects were admitted to the Texas Institute for Rehabilitation and Research as hospital patients for experimental studies, where they remained for a 1 month period. Three days prior to the first immersion period, the subjects were started on a controlled diet approximating 8-10 grams of salt intake daily and were required to spend the night in the hospital. At times during the day, when the subjects were not undergoing testing or participating in experimental studies, they were allowed to come and go from the hospital. They were required to eat all meals in the experimental ward, sleep at night in the ward, and keep an activity schedule approximating their schedule prior to being hospitalized.

At 5 p.m. on the day of conducting an experiment, the subjects were fed a low fat hospital meal, after which they were given no further food or water until the experimental period, which started at 10 p.m. that night and lasted until 10 a.m. on the following morning. At 10 p.m., the beginning of the experimental test condition, the subjects were given 400 ml. of water. They were fed a 400 ml. malt at 2 a.m. and at 8 a.m. during the experimental condition.

All water immersion experiments were of 12 hours duration. For the water immersion studies, the subjects were immersed in the head-out position, utilizing a life preserver around their necks with a strap encircling the buttocks to provide a bouyant effect to keep them in a semi-sitting position without requiring exertion or muscular effort by the subject. The temperature of the water was maintained at 93° F. ± 1° F.

TABLE I

SUBJECT CHARACTERISTICS

Subject Initials	Age (years)	Height (cm.)	Weight (kg.)
J.W.B.	22	172	64.2
L.G.B.	25	165	77.2
J.M.D.	21	170	74.9
G.G.G.	29	170	54.6
A.J.	34	173	70.3
R.R.R.	35	176	93.1

TABLE II

EXPERIMENTAL DESIGN

Water Immersion Periods	Subjects 1	2	3	4	5	6
1	A	F	E	D	C	B
2	B	A	F	E	D	C
3	C	B	A	F	E	D
4	D	C	B	A	F	E
5	E	D	C	B	A	F
6	F	E	D	C	B	A

Treatments

A Water Immersion, No Cuffs

B Water Immersion, No Cuffs

C Water Immersion, Arm Cuffs (1-minute-on, 1-minute-off)

D Water Immersion, Arm Cuffs (2-minutes-on, 4-minutes-off)

E Water Immersion, Arm Cuffs (5-minutes-on, 10-minutes-off)

F Water Immersion, Leg Cuffs (5-minutes-on, 10-minutes-off)

The arm and leg cuffs were inflated from separate sources of pressure; the arm cuffs were inflated to a pressure of approximately 60 to 70 mm. Hg, and the leg cuffs were inflated to a pressure of 120 mm. Hg to compensate for the balancing hydrostatic pressure effect due to the weight of the water above the level of the leg cuffs. Cuff treatment was employed as indicated, using a 3 3/4 inch wide cuff applied to the upper part of the thigh and arm depending upon the experimental condition.

Plasma Volume

Prior to and after each water immersion experiment, plasma volume determinations were performed using iodinated human serum albumin (I^{125} and I^{131}). Prior to injection of the isotope, a background sample of blood was withdrawn from each subject. Approximately 5 microcuries of radioisotope were injected into the antecubital vein of each subject, followed 15 minutes later by withdrawal of blood into a heparinized syringe from the opposite antecubital vein. Duplicate 1 ml. samples of plasma were counted. Hematocrit determinations were made in triplicate using a microcapillary technique.

Tilt Table Studies

Tilt table studies were performed before and after each experimental condition. In order to avoid the influence of circadian variations upon tilt response, the tilt prior to a given experimental condition was performed at approximately 1 p.m. the afternoon prior to the subjects' participation in the experiment which began at 10 p.m. that night. The subjects were tilted on completion of the experimental condition at 10 a.m. the following day. After the subject was considered to be in a baseline condition for the particular test circumstance, 5 minutes of control data were obtained with the subject in the horizontal position. The subject then was tilted manually in approximately 3 to 5 seconds to a 70° head-up tilt position. The subject was supported in the upright position by an English-saddle type support, with most of his body weight borne by his ischael tuberosities, thus providing a passive tilt. The subject was kept in the upright position for 20 minutes unless syncope or impending syncope occurred. After tilt down, an additional 5 minutes of control data were obtained.

Data were obtained continuously during the tilt procedure and recorded on a strip chart recorder and on magnetic tape for storage and future analysis. Electrocardiographic data were collected from NASA-type electrodes placed at the M-X and transthoracic sites. Respiration was measured with an impedance pneumograph connected to electrodes placed transthoracically. Cuff-microphone blood pressure measurements were obtained from the right arm, using apparatus to obtain automatic cuff inflation, cycled every 30 seconds.

Data Analysis

The heart rate data were determined by counting the total heart beats in each successive minute during the tilt procedure. Blood pressure measurements were arbitrarily and systematically collected at the beginning of each minute by reading the corresponding systolic and diastolic pressure. These heart rate and blood pressure data were analyzed as described in another paper.[6] For the heart rate and blood pressure information, a group of derived measurements were set up which would characterize the tilt response. An analysis of variance then was performed to select statistically significant changes which might characterize the effect of different treatments. The units for the derived measurements are as follows: heart rate (beats/minute), blood pressure (mm. Hg), slopes of lines fit to blood pressure (mm. Hg/minute), and time (minutes). The analysis of blood volume and other data utilized an analysis of variance, with the main effects of subject and treatment; also considered in the analysis was the interaction between the main effects.

RESULTS

In Table III are indicated the changes in the plasma volume for each of the periods of water immersion. A decline in plasma volume was found for all of the water immersion periods and all of the subjects except one. Although the pre-immersion and post-immersion plasma volume values are not indicated in this table, an analysis of variance was performed on the data using the main effects of subject, period, and treatment. There was not a significant difference in the plasma volumes after treatments or periods. There was significant difference in subject-to-subject values of the plasma volume both before and after water immersion. There was not a significant difference in the change in plasma volume for the main effects of subject, period, or treatment. In Table IV are shown changes in hematocrit of the subjects during the different waterimmersion studies. There was not a statistically significant difference in the changes for any of the treatment conditions.

In Table V are presented the means of tilt table measurements before the periods of deconditioning. As is indicated in Table II, a Latin Square experimental design was used for the assignment of treatments for each water immersion period. The data in Table V is presented to demonstrate any cumulative effect on the tilt table response due to the short spacing of the water immersion studies on Monday and Thursday of each week. An analysis of variance of the data did not show significant differences in the tilt table measurements for the tilts prior to each of the periods of deconditioning. The means for the data show the small day-to-day variation that is encountered in the tilt response of a group of individuals under controlled experimental conditions.

In Table VI are presented the means of tilt table measurements showing the effect of water immersion and cuff treatments. A total of 36 tilt table tests on six subjects before the six treatments are indicated in the first column. A total of six tilt table tests on the six subjects is given by the means indicated for each of the six treatments employed. The asterisks indicate the level of significance in the difference of pooled pre-water immersion tilt tests compared to the tilt tests after the treatments. The changes in the means reflect the characteristics

TABLE III

CHANGE* IN PLASMA VOLUME (ml.)

Subject Initials	Water Immersion	Water Immersion	Arm Cuffs 1min:1min	Arm Cuffs 2min:4min	Arm Cuffs 5min:10min	Leg Cuffs 5min:10min
	TREATMENT					
J.W.B.	149	554	287	246	293	645
L.G.B.	457	221	404	62	444	193
J.M.D.	431	649	425	120	345	242
G.G.G.	506	467	476	656	381	32
A.J.	71	621	105	-96	177	191
R.R.R.	273	398	239	406	368	153
MEAN	315	485	323	248	335	243

*Pre-immersion plasma volume minus post-immersion plasma volume

TABLE IV

CHANGE* IN HEMATOCRIT

Subject Initials	TREATMENT					
	Water Immersion	Water Immersion	Arm Cuffs 1min:1min	Arm Cuffs 2min:4min	Arm Cuffs 5min:10min	Leg Cuffs 5min:10min
J.W.B.	4.0	1.5	2.1	3.5	2.5	4.0
L.G.B.	6.3	4.3	2.5	4.6	4.5	2.7
J.M.D.	3.5	3.6	3.3	3.5	4.4	4.5
G.G.G.	6.2	3.7	4.0	2.2	1.2	5.0
A.J.	4.9	7.0	3.3	3.7	4.0	5.1
R.R.R.	4.0	3.0	3.0	4.2	6.5	5.6
MEAN	4.8	3.9	3.1	3.6	3.9	4.5

*Post-immersion hematocrit minus pre-immersion hematocrit

TABLE V

MEANS OF TILT TABLE MEASUREMENTS
BEFORE PERIODS OF DECONDITIONING

Measurement	Period of Deconditioning 1	2	3	4	5	6
Time to Tilt Down	21.0	21.0	21.0	21.0	21.0	21.0
Average HR Pre-tilt	72.4	77.7	75.6	72.2	72.1	71.3
Maximum HR During Tilt	93.3	100.2	99.8	93.7	93.3	92.2
Change in HR with Tilt	20.9	22.4	24.2	21.5	21.2	20.8
Fractional Increase in HR	0.30	0.29	0.33	0.30	0.31	0.29
Average PP Pre-tilt	50.6	54.9	58.4	51.7	51.5	50.3
Minimum PP During Tilt	33.5	31.5	35.7	32.2	33.0	34.0
Average Pre PP-Min During	17.1	23.4	22.8	25.6	18.5	16.3
Fractional Decrease in PP	0.34	0.42	0.39	0.43	0.36	0.32
Slope of Diastolic Pressure	0.22	0.25	0.09	0.33	0.70	0.10
Slope of Systolic Pressure	0.18	-0.26	-0.27	0.10	0.10	0.04
Slope of Mean Pressure	0.20	0.08	-0.03	0.25	0.50	0.08
Slope of Pulse Pressure	-0.04	-0.50	-0.36	-0.23	-0.59	-0.06

TABLE VI

MEANS OF TILT TABLE MEASUREMENTS SHOWING EFFECT OF WATER IMMERSION AND CUFF TREATMENT

Measurement	Pre-Tilts	TREATMENT Water Immersion	Water Immersion	Arm Cuffs 1:1	Arm Cuffs 2:4	Arm Cuffs 5:10	Leg Cuffs 5:10
Time to Tilt Down*	21.0	19.2	19.4	18.8	20.5	18.2	20.5
Average HR Pre-tilt**	73.6	67.3	66.5	68.5	67.9	66.6	64.9
Maximum HR During Tilt**	95.4	105.2	102.7	107.0	105.8	100.5	96.0
Change in HR with Tilt**	21.9	37.9	36.2	38.5	37.9	34.0	31.1
Fractional Increase in HR**	0.30	0.59	0.55	0.57	0.56	0.52	0.49
Average PP Pre-tilt**	53.9	40.7	44.7	43.3	47.3	42.9	44.6
Minimum PP During Tilt**	33.3	22.3	26.7	23.3	24.3	21.3	23.5
Average Pre PP-Min During	20.6	18.4	18.0	19.9	22.9	21.5	21.1
Fractional Decrease in PP*	0.38	0.45	0.39	0.46	0.46	0.50	0.47
Slope of Diastolic Pressure*	0.27	-1.52	-0.96	-0.56	-0.08	-1.45	0.35
Slope of Systolic Pressure*	-0.02	-0.98	-1.13	-2.10	-0.51	-1.86	-0.27
Slope of Mean Pressure*	0.18	-1.31	-1.02	-1.07	-0.23	-1.59	0.15
Slope of Pulse Pressure**	-0.29	0.64	-0.16	-1.53	-0.43	-0.41	-0.63

* $p < 0.05$

** $p < 0.01$

of water immersion deconditioning. The units for these measurements are as follows; time (minutes), heart rate (beats/minute), blood pressures (mm. Hg), and slopes of lines fit to blood pressure measurements (mm. Hg/minute). There were no occurrences of syncope in the pre-immersion tilts as is indicated by the time to tilt down. Syncope did occur in several of the subjects after the water immersion deconditioning. The average heart rate pre-tilt was lower following all periods of water immersion with or without cuff treatment. There is no statistically significant difference in the lowering of heart rate for the different treatment conditions. Compared to pre-immersion values, the maximum heart rate during tilt is elevated significantly following all periods of immersion. The value for this maximum heart rate is reflected further in the change of heart rate with tilt and the fractional increase in heart rate. The average pulse pressure pre-tilt is significantly lower after all water immersion treatments. Further, there is a significant narrowing of pulse pressure during tilt tests after immersion, as is reflected in the minimum pulse pressure during tilt. There is a significant difference in the slope of lines fit to blood pressure measurements as is indicated by more negative slopes after periods of deconditioning. None of the post-treatment means were significantly different from each other for any of the immersion experiments. The only significant differences observed were in the post-immersion values compared to the pre-immersion values.

DISCUSSION

An assessment of the values of different configurations of periodically inflated extremity cuffs in preventing or reducing the cardiovascular manifestations of deconditioning is facilitated in this experiment by the use of the same group of subjects for each of the experimental conditions. The use of a Latin Square experimental design minimizes any cumulative effects from successive periods of immersion, although this did not appear to be an important factor in this experiment. Careful control of the activities and diets of the subjects during the periods between immersion, with performance of the plasma volume and tilt table tests at the same time of day with respect to the immersion period probably added to the reproducibility observed in the tilt table tests.

The occurrence of cardiovascular deconditioning during water immersion is reflected in both the tilt table results and the decline in plasma volume. The tilt table tests were performed at approximately the same time each day to minimize any effect of circadian changes on this test procedure. The plasma volume determinations were performed immediately prior to water immersion and immediately after the 12 hour period of deconditioning. A decline was found in the mean plasma volume for all the experimental conditions. The effect of circadian changes on the plasma volume cannot be evaluated in this experiment, but a similar degree of changes in plasma volume has been observed in other water immersion experiments conducted at different times of the day. An increase in hematocrit was noted for the corresponding decline in plasma volume. The decline in plasma volume may be reflected in the tilt table changes observed after water immersion; however, the decline in plasma volume cannot be incriminated for all the observed manifestations of tilt table intolerance.

Cardiovascular deconditioning was manifested by significant changes in the maximum heart rate during tilt for all the treatments except leg cuffs. After these water immersion experiments, the maximum heart rate during tilt was not as great as has been seen following prolonged bedrest recumbency or space flight. The value for maximum heart rate during tilt may be influenced by the lowered average heart rate pre-tilt. The changes in heart rate with tilt and fractional increase in heart rate thus become more sensitive indicators of the changes in heart rate after immersion compared to before immersion.

The average pulse pressure pre-tilt is significantly lower after deconditioning and the minimum pulse pressure during tilt becomes narrower. Both of these could be reflections of the lower plasma volume after the deconditioning. The slopes of the blood pressure measurements are significantly different after the deconditioning, indicating a progressive downward trend of pressure during the tilt table procedures. This downward trend could reflect progressive pooling of blood or transudation of fluid from the vascular to the extravascular space of the lower extremities during the tilt procedure.

This water immersion experiment utilizing subjects in the head-out position produces definite cardiovascular deconditioning. There is no suggestive protective effect from the use of arm cuffs or leg cuffs for the timing cycles used. The reasons for the failure for protection in this experiment as compared to the experiments of Graveline[1] and Vogt[2,3] could be several fold. Graveline utilized subjects totally immersed with a pressure helmet for breathing, and used combined arm cuffs and leg cuffs. Other studies by the author have not indicated the combined cuffs to be more effective than only arm cuffs or leg cuffs, although a suggestive protective effect has been seen from the use of arm cuffs in the bedrest situation[8] with a cuff-timing cycle of 2-minutes-on, 4-minutes-off. In assessing the lack of protection from lower extremity cuffs, consideration must be given to the lack of effective transfer of cuff pressure to the venous system of the lower extremities by the relatively narrow cuffs; the significance of this factor cannot be evaluated in this experiment. Other studies[7] by the author using different cuff inflation - deflation timing cycles with leg cuffs and combinations of arm and leg cuffs likewise did not indicate significant prevention of the cardiovascular deconditioning of water immersion.

The use of only arm cuffs with an inflation-deflation cycle of 2-minutes-on, 4-minutes-off has been found to provide a suggestive protective effect in the bedrest and water immersion conditions. The amount of this protection from tilt intolerance in the bedrest experiments was small. The protective effect in water immersion experiments was only in preventing plasma volume changes rather than in preventing tilt table manifestations of cardiovascular deconditioning.

From these experiments, it is concluded that any protective effect offered by the use of intermittently inflated extremity cuffs is minimal in the prevention of cardiovascular deconditioning of water immersion as is manifested by a decline in plasma volume and tilt table intolerance. The failure to find definite protection in experimental conditions using either bedrest or water immersion to simulate weightlessness would make it logical to conclude that further consideration of the use of extremity cuffs in the space flight situation is not warranted. It is realized that the cardiovascular deconditioning associated with space flight may be different from that associated with water immersion or bedrest, but since definite tilt protection cannot be verified for the use of extremity cuffs in either of these two situations, it is not likely they would be protective in the flight situation. Further, the evaluation of the effectiveness or lack of effectiveness of cuffs in the space flight situation would be difficult because of the small number of subjects and the many other complicating factors that would enter into an evaluation of the plasma volume and tilt table changes in association with a flight.

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TILT TABLE AND PLASMA VOLUME CHANGES WITH SHORT TERM DECONDITIONING EXPERIMENTS

by

Fred B. Vogt, M.D.

INTRODUCTION

Studies have been conducted on normal subjects that demonstrate that cardiovascular deconditioning occurs with water immersion, prolonged bedrest, chair rest, or space flight. The mechanism or mechanisms responsible for the cardiovascular deconditioning seen with each of these situations is unclear. Numerous techniques have been evaluated for their protective effect in preventing or controlling the deconditioning that occurs in these simulated weightlessness experiments or in space flight. These techniques have included supine bicycle exercise, extremity cuffs with bicycle exercise, isometric exercises, Bungie Cord exercise, lower body negative pressure, periodic Flack maneuvers, other positive pressure breathing techniques, use of drugs, short arm centrifugation, other accelerative types of motions, and intermittent inflation of extremity cuffs.

In water immersion studies, Graveline[1], showed a protective effect against the tilt table intolerance by the use of extremity cuffs intermittently inflated using a 1-minute-on, 1-minute-off inflation-deflation cycle. Vogt,[6,7] in bedrest studies conducted in 1964, did not demonstrate a protective effect of lower extremity cuffs with an inflation-deflation cycle of 5-minutes-on, 10-minutes-off. Vogt[4] did interpret a partial protective effect from extremity cuffs inflated with a 1-minute-on, 1-minute-off, inflation-deflation cycle; and, because of the experimental design, interpreted the results as being due primarily to the cuffs inflated on the upper extremity. Vogt and Johnson[5] found an increased rate of disappearance of tagged albumin from the vascular system and a decline in plasma volume during water immersion, and suggested this as one possible contributing mechanism for the cardiovascular deconditioning seen with water immersion.

From the Texas Institute for Rehabilitation and Research, Houston, Texas. This research was conducted under sponsorship of the National Aeronautics and Space Administration, under Contracts NAS 9-1461 and NAS 9-5821. Computer services were provided at the Texas Medical Center, Regional Computer Facility, under sponsorship of NIH Grant FR 00254.

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The use of the extremity cuffs reduced the rate of disappearance of the tagged albumin and protected against the loss of plasma volume.

It was the purpose of the experiment reported herein to study further the mechanism of the protective effect seen with the use of intermittently inflated extremity cuffs comparing different cuff configuration and inflation times on the same group of subjects who underwent several water immersion experiments. In addition, short-term bedrest and chair rest experiments were conducted to contrast the results with the water immersion experiments.

METHOD

Subjects

Nine healthy adult male subjects participated in this study involving eight experimental conditions. Subject characteristics are presented in Table I. Subject B.J.H. participated only in the first two water immersion conditions and was replaced by subject J.Z.H. for the remainder of the test conditions. For each subject, a complete medical history was compiled, and a physical examination (with appropriate laboratory tests) was performed to exclude subjects with any conditions contraindicatory to their participation in the study.

Experiment Design

In Table II is shown the scheduling of the eight experimental conditions in which the subjects participated. The duration of each of these experimental conditions was 12 hours. For convenience in testing, the subjects were divided into two groups; group A consisted of subjects R.L.A., L.F.E., G.G.G., and A.J.P. Group B consisted of subjects L.E.D., B.G.H., J.Z.H., A.C.I., and H.G.R.

Experimental Protocol

The subjects were admitted to the Texas Institute for Rehabilitation and Research, where they remained for a 2 month period as hospital patients for experimental studies. Three days prior to the first immersion period, the subjects were started on a controlled diet approximating 8-10 grams salt intake daily and were required to spend the night in the hospital. At times during the day, when the subjects were not undergoing testing or participating in experimental studies, they were allowed to come and go from the hospital. They were required to eat all meals in the experimental ward, sleep at night in the ward, and keep an activity schedule approximating their schedule prior to being hospitalized.

At 5 p.m. on the day of conducting an experimental condition, the subjects were fed a usual hospital meal, after which they were given no further food or water until the beginning of the experiment, which started at 10 p.m. that night and lasted until 10 a.m. the following morning. At 10 p.m., the beginning

TABLE I

SUBJECT CHARACTERISTICS

Subject Initials	Age (yrs.)	Height (cm.)	Weight (kg.)	Occupation
A.J.P.	22	185	74.8	Marine veteran*
G.G.G.	28	172	55.7	Shop clerk
B.G.H.	22	174	88.9	Laborer
H.G.R.	28	175	77.8	Marine veteran*
R.L.A.	21	187	82.0	Student
L.F.E.	25	185	81.7	Student athlete
A.C.I.	24	163	54.3	Student athlete
L.E.D.	22	187	77.0	Army veteran*
J.Z.H.	27	183	73.4	Aircraft mechanic

*Unemployed

TABLE II

SCHEDULE OF EXPERIMENTAL CONDITIONS*

Week	Group 1	Group 2
1	A	B
2	C	A
3	E	F
4	F	E
5	H	G
6	G	H
7	B	C
8	D	D

*Experimental conditions

A	Water Immersion (W.I.)
B	W.I., Arm Cuffs only
C	W.I., Leg Cuffs only
D	W.I., Arm and Leg Cuffs
E	Bed Rest - 12 hours
F	Chair Rest - 12 hours
G	W.I., Leg Cuffs, last 4 hrs. W.I.
H	W.I., Leg Cuffs, 15 min./hr. for 12 hrs.

of the experimental test condition, the subjects were given 400 ml. of water. They were fed a 400 ml. malt at 2 a.m. and 8 a.m. during the experimental condition. Group A was tested on Monday night of each week, whereas group B was tested the following night.

All experimental conditions were of 12 hours duration. For the water immersion studies, the subjects were immersed in the head-out position, utilizing a life preserver around their necks with a strap encircling the buttocks to provide a bouyant effect to keep them in a semi-sitting position without requiring exertion or muscular effort. The temperature of the water was maintained at 93° F. $\pm$ 1° F. For the bedrest condition, the same pre-experimental conditions were used, and the subject was admitted to bedrest instead of water immersion. For the chair rest experiment, the subjects sat in office-desk type chairs for the 12 hour period, during which time they were allowed to read a book..

For the water immersion studies, the arm and leg cuffs were inflated from separate sources of pressure; the arm cuffs were inflated to a pressure of approximately 60-70 mm. Hg, and the leg cuffs were inflated to a pressure of 120 mm. Hg to compensate for the balancing hydrostatic pressure effect due to the weight of the water above the level of the leg cuffs. Cuff treatment was employed as indicated, using a 3 3/4 inch wide cuff applied to the upper part of the thigh and arm depending upon the experimental condition. The cuff inflation-deflation cycle was 2-minutes-on, 4-minutes-off, with the cuff being fully inflated in 5-8 seconds, throughout the 12 hour period for the experimental conditions, (a) arm cuffs only, (b) leg cuffs only, (c) both arm and leg cuffs. For the condition of leg cuffs only for the last 4 hours of water immersion, the leg cuffs were inflated to a pressure of 120 mm. Hg for the last 4 hours of immersion using the same 2-minutes-on, 4-minutes-off cycle. For the experimental condition of leg cuffs for 15 minutes per hour for 12 hours, the leg cuffs were inflated through three 2-minutes-on, 4-minutes-off cycles each hour with an inflation pressure of 120 mm. Hg. No cuff treatment was employed during the bedrest and chair rest experimental conditions.

Prior to and immediately after each experimental condition, plasma volume was determined using iodinated human serum albumin (I-125). Plasma volume determinations were not performed on subjects L.F.E. and A.C.I. because they had undergone repreated plasma volume determinations using isotopes in a different experiment. The procedure described was altered for them only in that a blank was injected in place of isotope. For each test, blood was obtained from the subject for the background isotope sample. Approximately 5 microcuries of radioisotope then were injected into the antecubital vein of each subject, followed 10 minutes later by the withdrawal of blood into a heparinized syringe from the opposite antecubital vein. Triplicate 1 ml. samples of plasma were counted for the volume determinations. Hematocrits were determined using a microcapillary technique using triplicate samples. Urine volume was collected over the 12 hour period.

Tilt Table Studies

Tilt table studies were performed before and after each experimental condition. In order to avoid the influence of circadian variations upon tilt response, the tilt prior to a given experimental condition was performed at approximately 2 p.m. the afternoon prior to the subjects' participation in the experiment which began at 10 p.m. that night. The subjects were tilted on completion of the experimental condition at 10 a.m. the following day.

After the subject was considered to be in a baseline condition for the particular test circumstance, 5 minutes of control data were obtained with the subject in the horizontal position. The subject then was tilted manually in approximately 3-5 seconds to a 70° head-up tilt position. The subject was supported in the upright position by an English-saddle type support, with most of his body weight borne by his ischael tuberosities, thus providing a passive tilt. The subject was kept in the upright position for 20 minutes unless syncope or impending syncope occurred. After tilt down, an additional 5 minutes of control data were obtained.

Data were obtained continuously during the tilt procedure and recorded on a strip chart recorder and on magnetic tape for storage and future analysis. Electrocardiographic data were collected using NASA-type electrodes placed at the M-X and transthoracic sites. Respiration was measured with an impedance pneumograph connected to electrodes placed transthoracically. Cuff-microphone blood pressure measurements were obtained from the right arm, using apparatus to obtain automatic cuff inflation cycled every 30 seconds.

Data Analysis

The heart rate data for the tilt tests were determined by counting the total heart beats in each successive minute during the tilt procedure. The first of two blood pressure measurements taken each minute were used in the analysis. These heart rate and blood pressure data were analyzed by an objective approach described in another paper[8]. For the heart rate and blood pressure information, a group of derived measurements were set up which would characterize the tilt response. An analysis of variance then was performed to select statistically significant changes which might characterize the effect of different treatments. The units for the derived measurements are as follows: heart rate (beats/minute), blood pressure (mm. Hg), slopes of lines fit to blood pressure (mm. Hg/minute), and time (minutes). The analysis of blood volume and other data utilized analysis of variance, with the main effects of subject and treatment; also considered in the analysis was the interaction between the main effects.

RESULTS

In Table III is indicated a summary of the means of the blood and urine findings for the different treatments on the seven subjects on whom isotope studies

TABLE III

MEANS OF PLASMA VOLUME, HEMATOCRIT AND URINE VOLUME CHANGES

Condition	Decrease* in Plasma Volume (ml.)	Increase* in Hematocrit(%)	Total Urine Volume (ml.)
Chair Rest	95	2.2	490
Bedrest	270	3.7	688
W.I., Arm Cuffs	291	1.7	481
W.I., Arm and Leg Cuffs	285	2.0	607
W.I., Leg Cuffs, last 4 hrs.	480	2.2	590
Water Immersion	564	3.2	990
W.I., Leg Cuffs	277	2.0	816
W.I., Leg Cuffs, 15 min./hr.	258	2.7	989

*Pre-condition value compared to post-condition value were performed. The data presented is on these seven subjects only to allow comparison of the three measurements. There was not any significant difference in the results obtained by including the additional two subjects on whom plasma volume determinations were not made because of previous exposure to isotope testing. The decrease in plasma volume was smallest during the 12 hour chair rest experiment, and greatest during the experiment utilizing water immersion without cuff treatment. However, there was not a statistically significant difference in the changes in plasma volume for the water immersion treatments with cuffs as compared to without cuffs, although as noted above, the greatest change in plasma volume occurred when cuffs were not used.

There was an increase in hematocrit during all experimental conditions. The greatest increase in hematocrit occurred after the water immersion experiment which did not utilize cuffs; this was the same treatment during which the greatest decline occurred in plasma volume. There was no statistically significant difference in the hematocrit changes in the water immersion experiments utilizing cuffs as compared to the water immersion experiments without the use of cuffs. The increase in hematocrit for the chair rest experiment paralleled that for the other water immersion experiments even though the plasma volume change was minimal.

In the third column of Table III is shown the total urine volume for each of the experimental conditions. The greatest diuresis occurred for the experimental condition of water immersion in which cuffs were not utilized. The smallest urine volumes were associated with the experimental conditions of chair rest and water immersion using arm cuffs. For the eight treatments, there was a statistically significant difference ($p < 0.05$) for the differences in urine volume for three experimental conditions compared to the other five; these were the treatments of (a) water immersion without cuffs, (b) water immersion, leg cuffs 15 minutes per hour, and (c) water immersion with leg cuffs. There was a correspondingly significant weight loss for the experimental conditions of water immersion without the use of cuffs. There were no significant weight gains or losses for the other experimental conditions.

In Table IV are indicated the means of tilt table measurements before and after the treatment periods. The pre-treatment values are pooled for convenience in presentation of the data, and thus represent a total of 64 tilt table measurements on the subjects for eight treatment periods. Each of the means describing tilt tests after the treatment periods represent a total of eight tilt table measurements. Compared to the pre-treatment tilt tests, there was significant difference in a number of the variables after the water immersion experiments; these changes are indicative of the type of cardiovascular deconditioning found with the different deconditioning techniques. The units for these measurements are as follows: time (minutes), heart rate (beats/minute), blood pressure (mm. Hg), and slopes of lines fit to pressure measurements (mm. Hg/minute).

There was no significant difference in the tilt table test performed after chair rest as compared to the pre-rest data. In fact, some of the variables changes in an opposite direction from that found with water immersion deconditioning; for example, the lowest maximum heart rate during tilt occurred in the post-chair rest situation.

TABLE IV

MEANS OF TILT TABLE MEASUREMENTS BEFORE AND AFTER TREATMENT PERIODS

				Water Immersion					
Variable	Pooled Pre-tilt	Chair Rest	Bed Rest	Arm Cuffs	Arm & Leg Cuffs	Legs last 4 hrs.	No Cuffs	Leg Cuffs	Leg Cuffs 15/hr.
Time to Tilt Down	25.9	26.0	24.7	24.1	25.0	25.4	23.0	25.1	20.4
Average HR Pre-tilt	70.8	65.7	66.6	66.4	66.1	64.8	65.2	68.8	64.7
Maximum HR During Tilt	98.1	89.8	97.3	105.3	102.3	103.1	105.9	109.1	99.6
Change in HR with Tilt	27.2	24.1	30.7	38.9	36.2	38.4	40.7	40.3	34.9
Fractional Increase in HR	0.39	0.38	0.47	0.61	0.56	0.61	0.62	0.59	0.54
Average PP Pre-tilt	57.3	55.2	54.5	54.5	51.8	50.3	49.6	50.4	49.6
Minimum PP During Tilt	28.4	25.3	27.5	22.3	19.9	16.4	18.9	18.7	18.8
Average Pre PP - Min During	28.9	29.9	27.0	32.2	32.0	34.0	30.7	31.7	30.9
Fractional Decrease in PP	0.50	0.55	0.51	0.59	0.60	0.67	0.62	0.63	0.61
Slope of Diastolic Pressure	0.10	0.20	-0.32	-0.02	-0.08	0.03	-0.61	-0.24	-1.50
Slope of Systolic Pressure	-0.18	0.09	-0.73	-0.60	-0.57	-0.47	-0.76	-1.03	-3.00
Slope of Mean Pressure	0.01	0.16	-0.45	-0.22	-0.24	-0.14	-0.66	-0.50	-2.00
Slope of Pulse Pressure	-0.28	-0.11	-0.41	-0.58	-0.49	-0.50	-0.15	-0.79	-1.50

There was an indication of cardiovascular deconditioning occurring in association with the bedrest treatment as is indicated by a shorter time to tilt down, a slightly larger change in heart rate with tilt, a significantly larger fractional increase in heart rate with tilt and more negative slope for the curves fit to the blood pressure measurements.

In general, the means of the measurements for the different water immersion conditions with and without cuffs do not differ significantly from each other. There is some condition-to-condition difference in some of the measurements used to characterize the tilt response. Most characteristic of the tilt table tests following the different water immersion treatments is the consistent difference from the pre-treatment tilt table tests, indicating the changes in the measurements characteristic of water immersion deconditioning.

There is a decline in the average heart rate pre-tilt during all of the experimental conditions. The maximum heart rate during tilt is elevated after all the water immersion deconditioning experiments except the one of water immersion with leg cuffs lasting 15 minutes per hour. The change in heart rate with tilt and the fractional increase in heart rate during tilt are significantly different from the pre-treatment tilt table determinations. The average pulse pressure pre-tilt is lowered after the water immersion treatments, as is the minimum pulse pressure during tilt. In general, the slopes of the lines fit to the blood pressure measurements are more negative for the different water immersion conditions after the treatment period. There is no specific pattern in the tilt table response that would indicate that any of the water immersion treatments with or without cuffs are significantly different from each other.

The occurrence of syncope or impending syncope was low for those experimental tests; of the 64 tilt table tests conducted prior to deconditioning treatments, there were two instances of syncope, and in the 64 tilt table tests conducted after the treatment periods, there were 13 instances of syncope. Six of the occurrences of syncope or impending syncope were observed in one subject.

DISCUSSION

The results of this study indicate that cardiovascular deconditioning, as manifested by a decline in plasma volume, an increase in hematocrit, and tilt table intolerance occurs with bedrest and water immersion experiments in as short a period of time as 12 hours. There is not a substantial change in the plasma volume and tilt table response after chair rest to indicate the occurrence of deconditioning with this form of treatment. The failure to observe deconditioning with chair rest is different from that reported by Lamb et al.[2,3]; however, in their chair rest experiments the duration of the studies was longer. It is of interest to note that deconditioning does occur in association with bedrest in as short a period of time as 12 hours, indicating that there are likely different mechanisms responsible for some of the manifestations of cardiovascular intolerance seen after bedrest and chair rest.

The declines in plasma volume for the different experimental conditions utilizing water immersion with or without extremity cuffs shows a gradation in response with the greatest loss occurring in water immersion without cuffs. However, an analysis of variance did not reveal a statistically significant difference in these values for the different treatments. Thus, one cannot definitely say that extremity cuffs protected against the decline in plasma volume seen with water immersion. Increases in hematocrit were observed corresponding to the declines in plasma volume. There was a somewhat greater increase in hematocrit for the chair rest situation than would be expected from the small decline in plasma volume. Since the plasma volume and hematocrit determinations were made immediately prior to and immediately after the deconditioning conditions, the effect of circadian variations on these measurements cannot be ruled out.

Compared to the other treatments, there was a statistically significant difference in the diuretic response for the conditions of water immersion, water immersion with leg cuffs 15 minutes per hour, and water immersion with the use of leg cuffs. There is no explanation for the apparent protection from this diuretic response in the other treatments where combinations of leg cuffs or arm cuffs were used. For example, the experimental condition in which leg cuffs were used only the last 4 hours showed a smaller diuretic response than observed with the continuous use of leg cuffs. Similarly, the use of combined arm and leg cuffs was associated with a greater diuretic response than with arm cuffs used alone. The smallest urine volume was associated with the two conditions of chair rest and water immersion with the use of arm cuffs.

The results of the tilt table tests indicated no significant difference in response to the different cuff treatments. It is interesting to note that the average heart rate pre-tilt is lower following all of the experimental treatments compared to before the treatment. A decline in heart rate has been noted previously in association with water immersion experiments, but there has usually been reported an increase in heart rate following long-term bedrest experiments. The tilt table tests were performed at approximately the same time of day and thus would minimize the circadian effect on this measurement. This indicates that perhaps the initial response during bedrest is a decrease in heart rate, with the increase occurring after a more prolonged period of recumbency.

There was no definite deconditioning evidenced in the tilt response after the chair rest deconditioning. In fact, the maximum heart rate during tilt was lowest after this treatment. There was evidence of cardiovascular deconditioning after the bedrest and water immersion treatments. Although not statistically significant, the results of the tilt table tests after the bedrest treatment did not demonstrate as much deconditioning as after the water immersion treatments. There was not a distinct separation in the results of the tilt table tests after the water immersion experiments with and without cuffs. One cannot conclude any protective effect from the use of cuffs in these water immersion experiments.

The results of this study are different from the protective effect found with the use of extremity cuffs in water immersion experiments reported by Graveline[1] and Vogt.[4,5] Other studies by Vogt and Johnson[10] showed a small protection from the use of upper extremity cuffs in the bedrest situation. The use of leg cuffs in the bedrest situation[6,7] did not show a protective effect. It would appear that the protective effect from intermittently inflated extremity cuffs is small for both the bedrest and water immersion conditions. The protection observed by Graveline could be related to the fact that his subjects used pressure helmets for breathing during total body immersion. The small protective effect observed by Vogt from upper extremity cuffs and not from lower extremity cuffs is unexplained. Perhaps the use of wider cuffs to provide a more effective transfer of cuff pressure to the veins of the lower extremity would have produced more positive results.

The results of this study would indicate that this group of subjects, deconditioned by head-out water immersion, did not derive any beneficial effect from the use of intermittently inflated extremity cuffs. It can be concluded that 12 hours of head-out water immersion produces definite cardiovascular deconditioning as manifested by a decline in plasma volume, increase in hematocrit and change in tilt table response. Chair rest of 12 hours duration produces a change in the tilt table response which has a trend opposite to that found after 12 hours of bedrest and water immersion. There are small and variable differences in the tilt table responses after different water immersion treatments, even using the same group of subjects. This treatment-to-treatment variability is greater than any trend of changes which would characterize protection afforded by the use of intermittently inflated extremity cuffs. Since no definite protective effect can be attributed to the use of lower extremity cuffs for the experimental condition of water immersion, it is unlikely that a significant protective effect would be found from the cardiovascular deconditioning that occurs in association with space flight. It is realized that different mechanisms may be responsible for the cardiovascular deconditioning that occurs in association with space flight. In addition, the small number of subjects participating in a space flight and the many factors that could influence the measurements characteristic of cardiovascular deconditioning would make an assesment difficult of the effectiveness of cuffs used during space flight.

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EFFECTIVENESS OF EXTREMITY CUFFS OR LEOTARDS IN PREVENTING OR CONTROLLING THE CARDIOVASCULAR DECONDITIONING OF BEDREST

by

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INTRODUCTION

Cardiovascular deconditioning as manifested in a decline of plasma volume and tilt table intolerance has been seen in association with studies to simulate weightlessness, as well as following orbital flight. Graveline[2] reported a protective effect from the tilt table manifestations of cardiovascular deconditioning associated with water immersion by use of intermittently inflated extremity cuffs. Vogt[3], and Vogt and Johnson[4], confirmed the apparent protective effect of extremity cuffs for the experimental condition of water immersion. Vogt[5], however, did not observe similar protective effect from intermittently applied extremity cuffs in the experimental condition of bedrest.

The studies by Vogt and Johnson suggested the possibility that protective effect of cuffs in water immersion experiments could occur with the use of arm cuffs only. In addition, the lack of effectiveness of the lower extremity cuffs in the bedrest situation may partially be attributed to the cuff timing cycle or width of the extremity cuffs.

Clinical studies have indicated that orthostatic hypotension can be controlled partially by the use of pressure garments to the lower body. Included in such studies have been the use of G-suits, leotard pressure garments, and elastic stockings. The mechanism of action of these protective techniques apparently results from the reduction in the amount of blood in the lower portion of the body to effectively augment the return of blood to the heart.

From the Texas Institute for Rehabilitation and Research, Houston, Texas. This study was conducted under sponsorship of the National Aeronautics and Space Administration under Contract NAS 9-5821. Computer services were provided at the Texas Medical Center, Regional Computer Facility, under sponsorship of NIH Grant FR 00254.

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It is the purpose of the study reported herein to evaluate further the effectiveness during bedrest of intermittently inflated extremity cuffs using arm cuffs only, and arm cuffs combined with leg cuffs, using a 2-minute-on, 4-minute-off inflation-deflation cycle. In addition, pressure garments (leotards) on the lower body were evaluated for their effectiveness in controlling the tilt table manifestations of cardiovascular deconditioning after bedrest.

METHOD

Subjects

Six healthy adult male subjects participated in three periods of 14 days bedrest conducted at the Texas Institute for Rehabilitation and Research in the summer of 1966. Subject characteristics are shown in Table I. For each subject, a complete medical history was compiled and a physical examination (with appropriate laboratory tests) was performed to exclude subjects with any condition contraindicatory to his participation in the experiment.

Experimental Design

A block diagram of the experimental design is shown in Figure 1. Each of the 2 week periods of recumbency was separated by 2 week periods to allow recovery of the subjects. The six subjects were divided into three groups for the assignment of the treatments of bedrest, bedrest using arm cuffs, and bedrest using arm and leg cuffs. There were thus two subjects in each of the three treatment groups for each of the three periods of bedrest, and each of the six subjects underwent three periods of bedrest.

Experimental Circumstances

The subjects were admitted to the Texas Institute for Rehabilitation and Research as patients for experimental studies. During their stay at the hospital they were fed regular hospital diets, the salt content of which approximated 8-10 grams daily. Fluid intake was *ad libitum*. In the interval between recumbency periods, the subjects were maintained on controlled diets and sleep schedules. In the daytime they were encouraged to follow an activity pattern similar to that followed prior to admission, except for the imposition of food and sleep control. During the period of recumbency, the subjects were required to remain flat in bed, were allowed one pillow under their heads, were allowed to roll from side to side in bed, and were allowed to turn on their sides to feed themselves.

When used, cuff treatment was employed 24 hours a day, using 3 3/4 inch wide cuffs applied to the upper part of the thigh or arm and inflated to a pressure of 70 mm. Hg. The cuff inflation-deflation cycle was 2-minutes-on, 4-minutes-off, with the cuff being fully inflated in 5-8 seconds. For each of the bedrest periods, two of the subjects had only arm cuffs applied while two had a combination of arm cuffs and leg cuffs. Assignment of the cuff treatments to the subjects in the three bedrest periods is shown in Figure 1.

TABLE I

SUBJECT CHARACTERISTICS

Subject Initials	Age (yrs.)	Weight (kg.)	Height (cm.)	Occupation
A.A.	30	71.4	182	Medical Technician
R.J.B.	22	77.2	190	Draftsman
L.L.L.	25	68.1	173	Student
D.L.M.	22	79.6	181	Student
E.J.P.	21	69.4	178	Student
J.A.S.	36	63.7	168	Research Assistant

Subject	1 2	3 4	5 6	
	A	B	C	Bedrest Period 1
	B	C	A	Bedrest Period 2
	C	A	B	Bedrest Period 3

Treatment

A Bedrest

B Bedrest using arm cuffs

C Bedrest using arm cuffs and leg cuffs

FIGURE 1

EXPERIMENTAL DESIGN

Tilt Table Studies

Tilt table studies were performed before and immediately after each period of recumbency. The tilt table tests were performed on each subject at the same time of day before and after the periods of recumbency, starting at 8 o'clock in the morning. The subject was given a light breakfast consisting of a glass of milk, eggs, and toast approximately 2 hours before his scheduled tilt table test. Electrocardiogram data were obtained continuously on a strip chart recorder and recorded on a magnetic tape for storage and future analysis. Blood pressure was obtained every 30 seconds using a cuff-microphone technique[1] for registration of blood pressure. Five minutes of control data were obtained with the subjects in the horizontal position after each subject was considered to be in a baseline position for the particular test circumstance. The subject then was tilted to the 70° upright position for a period of 15 minutes unless syncope or impending syncope occurred. The subject was supported in the upright position by an English-saddle type support with most of the body weight being borne by the ischael tuberosities, thus providing a passive tilt. After tilt down, an additional 5 minutes of control data were obtained. Two tilt tests were performed on each subject, both before and after bedrest. For the first tilt test, the subject wore elastic leotards* with a pressure of approximately 40 mm. Hg extending from the foot to the xyphoid region. These specially engineered garments were made for each individual by carefully measuring his body at one inch increments for the total length of the garment. The actual pressure under the garment was not measured. The garments were designed to provide a pressure of 40 mm. Hg when applied to a given circumference form along its entire length. It is probable that some variation in pressure occurred in different parts of the garment, but small variations in pressure were not considered to prevent the primary action of the garment. Only new garments were used in the entire study to rule out any changes in elasticity. After the first tilt test, the subject removed the leotards, and approximately 15 minutes later a second tilt was performed without the protective garment.

Plasma Volume

Plasma volume determinations were made in the morning prior to arising with the subjects in a fasting condition. Plasma volume determinations were made by the use of human iodinated serum albumin (I^{125}). Prior to injection of the isotope, a background sample of blood was withdrawn from the subject. Approximately 5 to 10 μc of radioisotope then were injected into the antecubital vein of each subject, followed 15 minutes later by withdrawal of blood into a heparinized syringe from the opposite antecubital vein. Duplicate 1 ml. samples of plasma were counted.

Data Analysis

Heart rate and blood pressure data were analyzed by an objective approach described by Vogt.[6] Heart rates were determined by counting the total heart beats in each successive minute during the tilt procedure; blood pressure measurements were selected at 1 minute intervals. From the heart rate and blood pressure

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information, a group of derived measurements were set up which would characterize the tilt response. An analysis of variance then was performed to determine the statistically significant changes which might characterize the effect of different treatments.

RESULTS

In Table II are shown the results of the plasma volume determinations. An analysis of variance did not reveal a significant difference in the plasma volume before the three bedrest periods, but the mean plasma volume was lowest prior to the treatment of recumbency with combined cuff treatment. There was a statistically significant ($p < 0.05$) decline in plasma volume for the treatment conditions of bedrest, bedrest with arm cuffs, and bedrest with arm and leg cuffs. The average decline in plasma volume was 279 ml. for the three treatments. The smallest decline in plasma volume occurred in association with the combined cuff treatment, but this decline was not statistically different from the decline in plasma volume for the other treatments.

In Tables III through VII are shown some of the results of the tilt table studies. The results of all analyses are not shown; only those measurements and results pertinent to the basic purpose of this study are indicated. The measurements characteristic of a tilt table response are described elsewhere.[6] The units for the measurements are as follows: time (minutes), heart rate (beats/minute), blood pressures (mm. Hg), and slopes of lines fit to blood pressure curves (mm. Hg/minute).

In Table III are indicated the means of tilt table measurements to demonstrate deconditioning for the three periods of recumbency; the non-leotard tilts pre-bedrest and post-bedrest were used in this evaluation. The effect of the potential treatment measures, which were randomly assigned, are not considered in this analysis. The asterisks beside the measurements indicate the level of statistical significance for the differences observed in the measurements pre-bedrest and post-bedrest. A total of 18 tilt table tests from six subjects were used in both the pre-bedrest and post-bedrest data. Compared to pre-bedrest values, there is a statistically significant increase after recumbency in the average heart rate pre-tilt, shown by an increase in heart rate from 65.3 to 72.6 beats/minute. Two subjects experienced syncope following one of the periods of recumbency, which is reflected in the shortened time to tilt down post-bedrest. The maximum heart rate during tilt is increased significantly after bedrest as compared to the pre-bedrest measurements. The increased heart rate with tilting is reflected further in the change in heart rate and fractional increase in heart rate. The average pulse pressure pre-tilt was not significantly different after bedrest as compared to before bedrest. There was not a statistically significant difference before and after bedrest in the minimum pulse pressure during tilt, but the minimum pulse pressure was smaller in the deconditioned subject. The average pulse pressure prior to tilt minus the minimum pulse pressure during the tilt was statistically different for the two times. The slope of the best line fit through the blood pressure measurements showed a consistent pattern; the slope of the lines fit to the diastolic blood pressure, systolic blood pressure, mean pressure, and pulse pressure were all negative after bedrest compared to a positive slope of the lines before bedrest, indicating the

sig. resting heart rate

TABLE II

PLASMA VOLUME (ml.)

Subject Initials	Bedrest		Bedrest Arm Cuffs		Bedrest Arm and Leg Cuffs	
	Pre	Post	Pre	Post	Pre	Post
A.A.	3981	3327	4149	3418	3854	3627
R.J.B.	4885	3534	4105	3612	3672	3837
L.L.L.	3144	3218	3356	3173	3045	3138
D.L.M.	3364	3146	3412	3111	3540	3246
J.A.S.	2521	2318	2466	2598	2508	2463
E.J.P.	3476	3155	3573	3432	3666	3400
Mean	3562	3116	3510	3224	3381	3285

TABLE III

MEANS OF TILT TABLE MEASUREMENTS TO DEMONSTRATE DECONDITIONING

Measurement***	Pre	Post
Time to Tilt Down	21.0	20.7
Average HR Pre-tilt**	65.3	72.6
Maximum HR During Tilt**	93.4	113.3
Change in HR with Tilt**	28.1	40.7
Fractional Increase in HR**	0.44	0.58
Average PP Pre-tilt	45.7	47.1
Minimum PP During Tilt	25.8	22.2
Average Pre PP-Min During*	20.0	25.0
Fractional Decrease in PP	0.42	0.52
Slope of Diastolic Pressure	0.01	-0.20
Slope of Systolic Pressure	0.04	-0.41
Slope of Mean Pressure*	0.02	-0.27
Slope of Pulse Pressure	0.02	-0.21

* $p < 0.05$

** $p < 0.01$

*** Measurements are for non-leotard tilts and are used to compare pre-bedrest tilts (pooled) with post-bedrest tilts (pooled).

change in pressures which are characteristic of deconditioning. Only the slope of the line fit to mean pressure showed a significant ($p < 0.05$) difference after deconditioning.

In Table IV are shown the means of the tilt table measurements before and after bedrest with various treatments. This analysis distinguishes the effect of different cuff treatments assigned during bedrest. The results of a total of 18 non-leotard tilts on six subjects are pooled for the pre-bedrest measurements; the results of six non-leotard tilt tests on the six subjects after the various treatments are compared to these pooled pre-bedrest measurements. There was not a statistically significant difference in the measurements following the three treatment conditions. After the arm cuff treatment, there was a smaller increase in heart rate during bedrest, the maximum heart rate during tilt was less, and the decrease in pulse pressure during tilt was less. For this same treatment, the slopes of the lines fit to blood pressure measurements were more negative. There was a statistically significant difference in all the heart rate measurements after bedrest compared to before bedrest for all three treatment conditions.

In Table V are shown the means of the tilt table measurements comparing pre-recumbency non-leotard tilts with leotards and non-leotards. This comparison is made to demonstrate both the deconditioning that occurred with bedrest recumbency and the protective effect afforded by the use of leotards. A total of 18 tilt tests in six subjects are used to determine the means presented. There is no significant difference in the time to tilt down using the post-bedrest leotard and non-leotard tilts. The average heart rate pre-tilt is highest after bedrest for the tilts which used leotards. The maximum heart rate during tilt after bedrest is statistically lower with the use of leotards as compared to the non-leotard tilts; but this value is still slightly higher than the non-leotard tilt prior to bedrest. The average pulse pressure pre-tilt is higher with leotards and the minimum pulse pressure during tilt does not drop as low with the use of leotards. The slopes of the lines fit to the blood pressure measurements are negative for both the leotard and non-leotard tilts after bedrest.

In Table VI are shown the means of tilt table measurements presented to compare leotard and non-leotard tilts in conditioned subjects. A total of 12 tilt table tests on six subjects are included for each type of tilt procedure. As is indicated by the asterisks, a contrast of the leotard and non-leotard tilts shows a statistically significant difference in several of the measurements in conditioned subjects. These data were different from the pre-bedrest data presented in the other tables. The average heart rate pre-tilt is slightly higher for the tilts in which leotards are used as compared to the non-leotard tilts, although this difference is not statistically different. There is a statistically significant ($p < 0.01$) difference in the maximum heart rate obtained during the tilt procedure for the two types of tilts; a lower maximum heart rate during tilt is found when leotards are used. The minimum pulse pressure during tilt does not reach as low a value ($p < 0.01$) when leotard tilts are compared to the non-leotard tilts. Further, the slopes of the blood pressure measurements are negative for the tilt procedure in which leotards were not utilized.

As is shown in Table VII, similar changes in heart rate were observed in deconditioned subjects for the contrast between the leotard and non-leotard tilts.

TABLE IV

MEANS OF TILT TABLE MEASUREMENTS BEFORE AND AFTER BEDREST WITH TREATMENTS

Measurement*	Pooled Pre-Bedrest	Post Bedrest	Post Arm Cuffs	Post Arm and Leg Cuffs
Time to Tilt Down	21.0	20.6	20.6	21.0
Average HR Pre-tilt	65.3	72.1	70.2	75.5
Maximum HR During Tilt	93.4	116.7	109.8	113.3
Change in HR with Tilt	28.1	44.5	40.0	37.9
Fractional Increase in HR	0.44	0.63	0.58	0.53
Average PP Pre-tilt	45.7	47.8	44.7	48.9
Minimum PP During Tilt	25.8	20.3	23.5	22.7
Average Pre PP-Min During	20.0	27.5	21.2	26.2
Fractional Decrease in PP	0.42	0.57	0.47	0.53
Slope of Diastolic Pressure	0.01	-0.13	-0.24	-0.23
Slope of Systolic Pressure	0.04	-0.16	-0.72	-0.35
Slope of Mean Pressure	0.02	-0.14	-0.40	-0.27
Slope of Pulse Pressure	0.02	-0.03	-0.48	-0.12

* Measurements are from non-leotard tilts only

TABLE V

MEANS OF TILT TABLE MEASUREMENTS COMPARING PRE AND POST-BEDREST TILTS

Measurement	Pre Non-Leotard	Post Leotard	Post Non-Leotard
Time to Tilt Down	21.0	20.4	20.7
Average HR Pre-tilt	65.3	76.2	72.6
Maximum HR During Tilt	93.4	97.9	113.3
Change in HR with Tilt	28.1	21.7	40.7
Fractional Increase in HR	0.44	0.30	0.58
Average PP Pre-tilt	45.7	50.8	47.1
Minimum PP During Tilt	25.8	30.6	22.2
Average Pre PP-Min During	20.0	20.2	24.9
Fractional Decrease in PP	0.42	0.39	0.52
Slope of Diastolic Pressure	0.01	-0.30	-0.20
Slope of Systolic Pressure	0.04	-1.51	-0.41
Slope of Mean Pressure	0.02	-0.71	-0.27
Slope of Pulse Pressure	0.02	-1.28	-0.21

TABLE VI

MEANS OF TILT TABLE MEASUREMENTS TO COMPARE LEOTARD AND NON-LEOTARD TILTS IN CONDITIONED SUBJECTS

Measurement	Leotard	Non-Leotard
Time to Tilt Down	21.0	21.0
Average HR Pre-tilt	68.2	66.5
Maximum HR During Tilt**	83.4	94.2
Change in HR with Tilt**	15.2	27.7
Fractional Increase in HR**	0.24	0.43
Average PP Pre-tilt	46.9	46.4
Minimum PP During Tilt**	30.4	24.8
Average Pre PP-Min During*	16.4	21.7
Fractional Decrease in PP**	0.34	0.46
Slope of Diastolic Pressure	0.06	-0.10
Slope of Systolic Pressure	0.21	-0.22
Slope of Mean Pressure	0.11	-0.14
Slope of Pulse Pressure	0.16	-0.12

* $p < 0.05$
** $p < 0.01$

TABLE VII

MEANS OF TILT TABLE MEASUREMENTS TO COMPARE LEOTARD AND NON-LEOTARD TILTS IN DECONDITIONED SUBJECTS

Measurement	Leotard	Non-Leotard
Time to Tilt Down	20.4	20.7
Average HR Pre-tilt	76.2	72.6
Maximum HR During Tilt*	97.9	113.3
Change in HR with Tilt**	21.7	40.7
Fractional Increase in HR**	0.30	0.58
Average PP Pre-tilt	50.8	47.1
Minimum PP During Tilt**	30.6	22.2
Average Pre PP-Min During	20.2	24.9
Fractional Decrease in PP**	0.39	0.52
Slope of Diastolic Pressure	-0.30	-0.20
Slope of Systolic Pressure**	-1.51	-0.41
Slope of Mean Pressure	-0.71	-0.27
Slope of Pulse Pressure*	-1.28	-0.21

* $p < 0.05$
** $p < 0.01$

A total of 18 tilt tests on six subjects were used for each type of tilt test. The average heart rate pre-tilt again was higher for the tilt in which leotards were used. The maximum heart rate during tilt was higher statistically ($p < 0.05$) for the tilts in which leotards were not used. This increase in heart rate during tilt also is reflected in a statistically significant ($p < 0.01$) difference in the fractional increase in heart rate for the leotard and non-leotard tilts. The minimum pulse pressure during tilt is higher statistically ($p < 0.01$) for the leotard tilt as compared to the non-leotard tilt. This pulse pressure change also is reflected in the fractional decrease in pulse pressure which is statistically ($p < 0.01$) lower when leotards are used. In contrast, the slopes of the lines fit to the blood pressure curves are more negative when leotards are used, but this difference is not statistically different.

DISCUSSION

The plasma volume changes in this study are in agreement with the findings in previous bedrest studies in which there was observed a decline in plasma volume with recumbency. There was not a statistically significant difference in the change of plasma volume for the three experimental conditions of bedrest, bedrest with arm cuffs, and bedrest with arm cuffs plus leg cuffs. Although the change in plasma volume for the condition of bedrest with arm and leg cuffs was less than for the other two experimental conditions, this reflected primarily a lower mean plasma volume prior to recumbency. While the mean plasma volume was lower prior to the treatment using combined cuffs, there was not a statistically significant difference in the post-bedrest plasma volumes for the three treatment conditions. Other studies[8] in our laboratory have indicated good reproducibility of measurements using the plasma volume technique described; for six plasma volume measurements obtained on a group of 12 subjects, the results indicated a 95% confidence interval of $\pm$ 8% about the mean.

The results of the tilt table studies are presented to demonstrate the cardiovascular deconditioning that occurs with bedrest, the differences in response in the leotard and non-leotard tilts for both conditioned and deconditioned subjects, and the effectiveness of the extremity cuffs in protecting against the tilt table manifestations of cardiovascular deconditioning. The experimental design is complicated somewhat by the use of two successive tilts in the pre-bedrest and post-bedrest conditions. The leotard tilt was selected to precede the non-leotard tilt, since it was thought the pressure garment would minimize any tendency for extravasation of fluid from the vascular to extravascular space during the tilt procedure. However, in this experiment, one cannot assess any beneficial or detrimental effect that may have resulted from the leotard tilt preceding the non-leotard tilt. Previous studies[7] by the author on conditioned subjects and those deconditioned by short-term water immersion have demonstrated minimal changes in three successive tilts performed without the use of leotards. After water immersion experiments, the primary difference in the successive tilts was noted in the rapidity with which the heart rate changes occurred, there being a more rapid change to a rather fixed maximum value during tilt for successive tilt tests. It was thought that the small difference that could result from successive tilts would be offset by the potential information gained from using the same subjects in the same state of conditioning or deconditioning to obtain comparative tilts. Other experimental studies[11] in our laboratory have indicated excellent day-to-day reproducibility of tilt table results on subjects under controlled dietary and activity schedules.

As is shown in Table III, there is definite deconditioning with the periods of recumbency. Only data from the non-leotard tilts are used in this evaluation to reduce any complication which would result from pooling data of both leotard and non-leotard tilt tests. Similar comparisons could have been presented for the leotard tilt tests pre-bedrest and post-bedrest; the results would have been of the same general nature, but the contrast between the pre-bedrest and post-bedrest values would not have been as great. After bedrest, the average heart rate pre-tilt is significantly elevated over the pre-bedrest values. This heart rate increase has been observed in other deconditioning experiments including recumbency and space flight; in contrast, the average heart rate has usually been found to be lowered in association with water immersion deconditioning. There is an accentuation of this increase in resting average heart rate pre-tilt with the use of leotards; the increase with leotards being greater after bedrest compared to before bedrest. The decline in plasma volume may be reflected in this measurement. The mechanism for this increase in heart rate associated with the use of leotards is not clearly understood; part of the change may be a reflection of the successive tilt procedures resulting in an overshoot or lowering of the heart rate after the first tilt which always utilized leotards.

There is a statistically significant difference in the tilt response using leotards as compared to not using leotards for both the conditioned and deconditioned subjects. Table V is presented to demonstrate the effectiveness of leotards in controlling the tilt table manifestation of the deconditioned state by comparing the leotard tilt response in the deconditioned state to the tilt response without the use of leotards in the conditioned state. There is a very significant increase in the average heart rate pre-tilt after deconditioning with the use of leotards. It appears that the protection afforded by the use of leotards is reflected in the action on mechanisms other than that responsible for control of the resting heart rate. There is a slight elevation of the maximum heart rate during tilt with use of leotards after bedrest compared to non-leotard tilts before bedrest. In deconditioned subjects, the maximum heart rate during the tilt with leotards is significantly lower than the maximum heart rate without the use of leotards. There is a further evidence of protection from the use of leotards in the maintenance of pulse pressure during the tilt test. The use of leotards does not prevent the declining blood pressure during tilt; the slopes of the lines fit to the blood pressure measurements are more negative in deconditioned subjects for tilt tests in which the subject wore leotards than in tilt tests without the use of leotards. This progressive decline in pressure as reflected in the slope measurements for the leotard tilt tests could reflect progressive changes that occur during the first tilt (leotards) with no progressive change occurring in the second tilt (non-leotard). Some variability in the slope measurements for lines fit to the pressure curves could result from the inaccuracies of taking blood pressure using the indirect cuff-microphone technique. The systolic and diastolic measurements are separated by the time taken for pressure to decline in the blood pressure cuff. Also, there tends to be an oscillatory change in blood pressure during tilts of deconditioned subjects which makes it difficult to define representative blood pressures.

There is not a statistically significant protective effect against cardiovascular deconditioning afforded by the use of intermittently inflated cuffs on the extremities. The mechanism for the apparent protective effect of extremity cuffs in other studies cannot be identified. It was thought previously that possible mechanisms of action of the extremity cuffs were to elevate the venous pressure and prevent the transfer of extravascular fluid back into the vascular space as well as to provide periodic stimulation of the venous system to maintain the venomotor tone. This mechanism can neither be confirmed nor denied. The failure to observe a protective effect from the use of intermittently inflated lower extremity cuffs[5] in previous bedrest studies could have resulted from the use of a cuff inflation-deflation cycle of 5-minutes-on, 10-minutes-off, for the cuff as well as from the use of cuffs only on the lower extremities. Consideration also might be given to the diminished effectiveness of the transfer of cuff pressure to the large portion of the lower extremities from the use of narrow cuffs. Other studies by the authors,[3,4] have suggested the protective effect could result from the use of cuffs only on the upper extremities. Other water immersion studies by the authors,[8,9] which have not been published, have indicated in one experiment a suggestive protection from the use of extremity cuffs, while a failure of protection was observed in another experiment. At this time, the evidence suggests that extremity cuffs may be partially protective for the bedrest and water immersion condition, but that this protection is not of such a degree to warrant their use in the space flight.

From this experiment it can be concluded that cardiovascular deconditioning did occur with recumbency, that there is not a significant protective effect from the use of intermittently inflated extremity cuffs, and that the use of leotards favorably alters the tilt response of both conditioned and deconditioned subjects.

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THE EFFECT OF INTERMITTENT LEG CUFF INFLATION AND INTERMITTENT EXERCISE ON THE TILT TABLE RESPONSE AFTER TEN DAYS BED RECUMBENCY

by

Fred B. Vogt, M.D.

Studies of the tilt table response of normal individuals date back to the turn of the century. Abnormal responses have been noted in a variety of circumstances, but the condition of cardiovascular deconditioning has aroused interest in recent years in aerospace medicine. Cardiovascular deconditioning generally is described as an ill-defined syndrome characterized by deterioration of normal compensatory reflexes or mechanisms as a result of experimental conditions which simulate various aspects of weightlessness. Deconditioning experiments have included bedrest, chair rest, water immersion, and space flight.

The usual response, upon change of a normal subject from the horizontal to the vertical position, is an increase in heart rate, a slight increase in diastolic pressure, and a slight decrease in systolic pressure. Cardiovascular deconditioning usually is said to occur after some experimental circumstance that alters the usual compensatory responses resulting in more pronounced changes in heart rate, a more rapid decrease in blood pressure, and the ultimate occurrence of signs and symptoms of syncope or impending syncope. It should be noted, however, that progressive changes in heart rate and blood pressure resulting in syncope, usually of the vasovagal type, occur in a fair proportion of healthy young adult males.

Various theories have been proposed to explain the mechanism resulting in cardiovascular deconditioning, including decrease in blood volume, sluggish venomotor reflexes that result in pooling of blood, and loss of muscle tone because of physical inactivity associated with the deconditioning experiment.

Various techniques have been used during deconditioning experiments in an attempt to prevent the development of tilt table manifestations of deconditioning. The studies of Deitrick, Whedon, and Shorr[5,17] showed some protective effect was derived from periodic rocking beds. Miller, et al.[7] interpreted some protection from a combination of various treatments of preconditioning, exercise, and head-up bed position. Vogt, et al.[11] found no definite protective effect from the performance of periodic Flack procedures during bedrest. Vallbona, et al.[10] found a suggestive protective effect from

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intermittent large doses of isometric exercise.[1] White and his group[18] interpreted the difference in tilt table response of two groups of subjects, one of which was subjected to periodic short-arm centrifugation, as evidence of its efficacy in reducing manifestations of cardiovascular deconditioning.

The equipment needed and the complexity of some of the techniques which must be applied to provide small amounts of protection make their usefulness somewhat limited in the manned space flight situation. Graveline[6] found a rather remarkable protective effect using intermittently inflated pressure cuffs on the four extremities of subjects normally deconditioned by short-term immersion in water. Vogt[12] confirmed this protective effect in water immersion experiments, and suggested that his results occurred primarily as a result of inflation of cuffs on the upper extremities. Also, Vogt and Johnson[13] have presented evidence that the difference in response may be associated with an abnormal transfer of a protein-fluid-electrolyte complex out of the vascular system into the extravascular space to account for part of the observed changes of deconditioning.

The purpose of the study reported herein was to evaluate the potential protective effect of two techniques which could be adapted to the manned space flight situation. Periodic use of a Bungie-cord exerciser, of the type used as a cardiovascular provocative test in Project Mercury, was selected as one method, since physical inactivity with decrease in muscle tone has been incriminated by some investigators as a possible mechanism of deconditioning. The other technique was periodic inflation of leg cuffs on the lower extremities to determine if a protective effect could be found in the bedrest situation as is found with water immersion. Cuffs were applied only to the lower extremities to simulate the experimental inflight experiment, M-1, planned by NASA for manned Gemini space flights. A cuff inflation-deflation cycle of 5-minutes-on, 10-minutes-off was selected, as it required less air for inflation, and previous venous catheterization studies by the author had indicated that several minutes of cuff inflation were required to obtain a significant increase in venous pressure. At the time of experimental design, the hypothesis was that periodic inflation of leg cuffs would increase venous pressure and thus result in a decreased transfer of fluid from the extravascular space into the vascular system. Such a technique also would provide periodic stimulation of venous reflex mechanisms from the periodic increase in venous pressure and the consequent pooling of blood.

METHOD

Subjects

Eleven healthy young adult male subjects participated in three periods of 10 days bedrest conducted at the Texas Institute for Rehabilitation and Research in the summer of 1964. Subject characteristics are shown in Table I. Subject A.P.K. participated in the first period of recumbency only and was replaced by subject L.F.E. Subjects who actively and regularly participated in physically competitive sports were classified as athletes. The other subjects were designated non-athletes.

TABLE I

Subject Characteristics

Subject Initials	Hospital Number	Age (yrs.)	Weight* (kg.)	Height* (cm.)	BSA** ($m.^2$)	Occupation
M.A.C.	70020	23	65.3	177.8	1.81	Student (NA)
L.F.E.****	70028	24	74.3	188.0	2.00	Student (A)
R.S.H.	70021	22	65.2	172.4	1.77	Student (A)
J.A.H.	70022	23	81.1	179.0	2.01	Student (NA)
B.E.H.	70019	21	69.8	177.8	1.88	Student (NA)
A.C.I.	70018	22	51.0	163.0	1.52	Student (A)
A.P.K.***	70023	24	59.4	174.0	1.72	Student (NA)
W.F.M.	70024	23	66.4	171.0	1.78	Student (NA)
C.E.R.	70025	25	80.6	192.4	2.11	Student (A)
G.S.R.	70026	26	65.6	177.8	1.83	Student (A)
R.R.T.	70027	22	78.2	172.4	1.92	Student (NA)

A Athlete
NA Non-athlete
* At the beginning of the experiment
** Dubois Body Surface Chart (prepared by Boothby and Sandiford)
*** Participated only in the first period of bedrest.
**** Participated only in the second and third periods of bedrest

Calendar of Experimentation

The calendar of experimentation is shown in Figure 1. The subjects were divided into two groups for convenience in testing; and, one group went into bedrest a day before the other group. Accordingly, the first group of subjects was ambulated one day earlier than the second group. During the first recumbency period half of the subjects performed periodic Bungie-cord exercises[2,3] and the remainder of the subjects had cuffs periodically inflated on their lower extremities. During the second period of recumbency, the treatments were reversed for the two groups of subjects. Finally, during the third period of recumbency, all subjects went through a period of bedrest without any preventive or treatment measure to define the effect of the experimental condition of bedrest. A detailed presentation of the experimental protocol is presented elsewhere.[4,14]

Experimental Circumstance

The subjects were admitted to the Texas Institute for Rehabilitation and Research as patients for experimental studies. During a 94-day stay at the hospital, they were fed controlled diets, the salt content of which approximated 8-10 grams daily. Fluid intake was ad libitum. In the intervals between recumbency periods, the subjects were maintained on controlled diets and sleep schedules. In the daytime, they were encouraged to follow activity patterns similar to that followed prior to admission, except for the imposition of food and sleep control. During the periods of recumbency, the subjects were required to remain flat in bed, were allowed one pillow under their heads, were allowed to roll from side to side in bed, and were allowed to turn on their sides to feed themselves.

Cuff treatment was employed 24 hours a day, using 3.75 inch wide cuffs applied to the upper part of the thigh and inflated to a pressure of 70-75 mm. Hg. The cuff inflation-deflation cycle was 5-minutes-on, 10-minutes-off, with the cuff being fully inflated in 5 to 8 seconds. Bungie-cord exercises were performed hourly for 10 treatment periods a day, starting at 8 a.m. The subject performed exercises in the horizontal position by placing his feet in a bracket at one end of the rubber Bungie-cord exerciser to provide a fixed point against which to pull. The subject kept his legs in a partially flexed position at this time to provide muscular exercise to the lower as well as the upper extremities. The extent or length of pull allowed for each exercise was determined for each subject prior to bedrest by selecting an exercise load which produced a moderate amount of cardioacceleration in response to the exercise. The exercise consisted of 120 pulls on a prescribed Bungie-cord, at a rate of one pull per second.

Tilt Table Studies

Tilt table studies were performed before and immediately after each period of recumbency. Electrocardiographic data were obtained continuously with a strip chart recorder and recorded on magnetic tape for storage and future analysis. Intra-arterial blood pressure measurements were obtained from the right brachial artery through a Cournand needle connected to a Statham pressure transducer. Other measurements were made, including forearm blood flow, venomotor tone, leg circumference changes, plasma volume changes, etc.; but, for simplicity, these measurements will not be considered here.

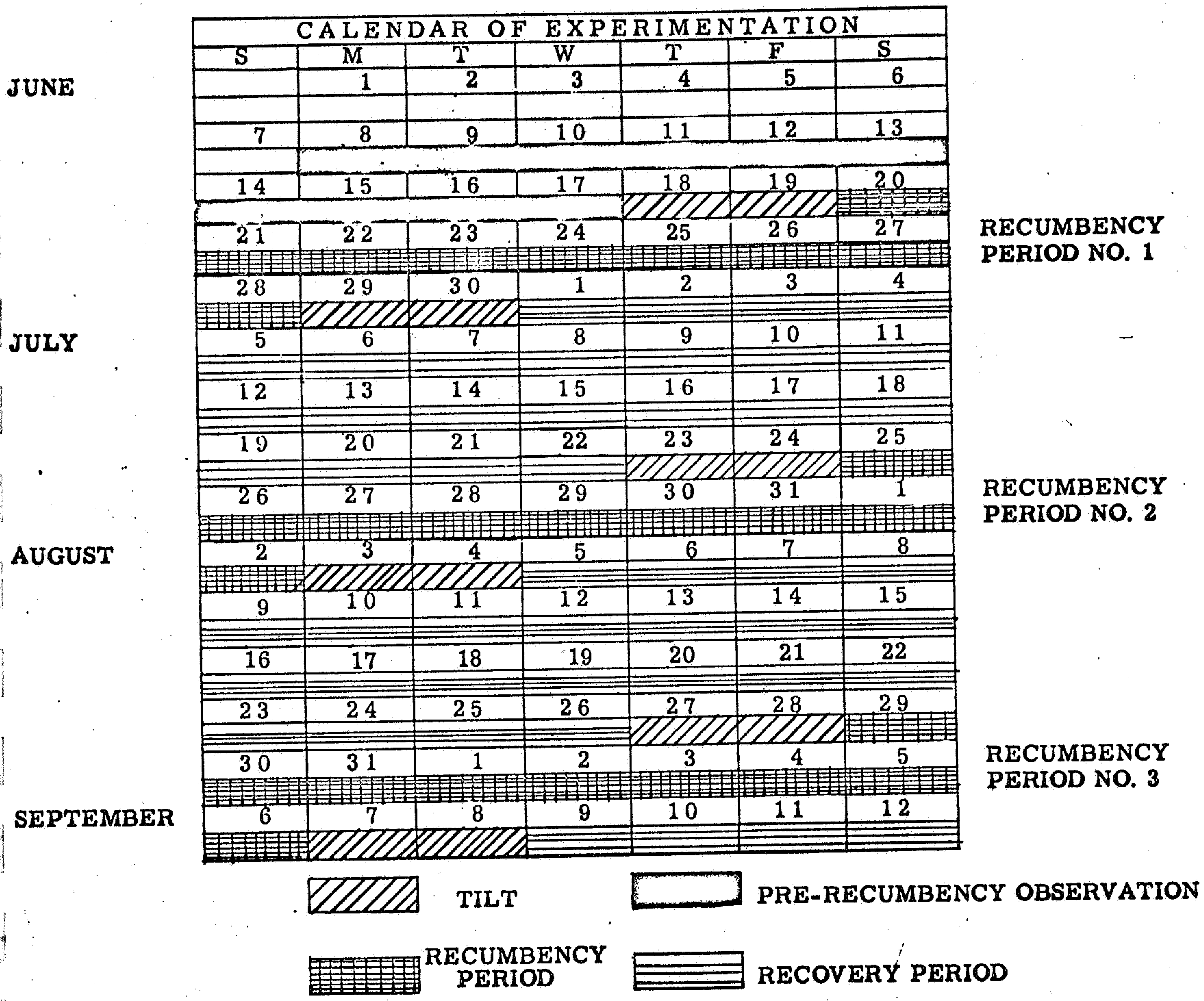

Figure 1. Calendar of Experimentation

Five minutes of control data were obtained with the subject in the horizontal position after the subject was considered to be in a baseline condition for the particular test circumstance. A Flack maneuver then was performed, and 5 minutes later the subject was tilted manually, taking approximately 3 to 5 seconds, to a 70° head-up tilt position. The subject was supported in the upright position by an English-saddle type support, with most of the body weight being borne by the ischeal tuberosities, thus providing a passive tilt. The subject was kept in the upright position for 20 minutes, unless syncope or impending syncope occurred. After tilt down, an additional 5 minutes of control data were obtained, followed by a repeat Flack maneuver, and the collection of 5 minutes of additional data. A schematic of the tilt procedure is shown in Figure 2. In Figure 3 a subject is shown on a table tilted to the 70° position.

Data Analysis

Heart rate and blood pressure data were analyzed by an objective approach described by Vogt.[15] Heart rates were determined by counting the total heart beats in each successive minute during the tilt procedure. Blood pressure measurements were arbitrarily and systematically collected exactly at the beginning of each minute by reading the corresponding systolic and diastolic blood pressures. The pre-tilt control data is represented by the 5 minutes of data collected prior to the Flack test, and the post-tilt data by the 5 minutes immediately following tilt down. For simplicity of discussion, the Flack maneuvers will not be considered in this paper.

From the heart rate and blood pressure information, a group of derived measurements were set up which would characterize the tilt response. An analysis of variance then was performed to select statistically significant changes which might characterize the effect of different treatments. The determination of analysis of variance utilized two main effects (treatment and non-athlete/athlete) and the interaction between the two to determine the residual term.

RESULTS

The results presented in this paper refer only to the studies conducted on the nine subjects who participated in all phases of the study. A summary is presented in Table II of the F values and significance levels for the measurements selected to describe characteristics of the tilt table response from this experiment. The basis for selection of these measurements is described elsewhere.[15] In the first column are the statistical comparisons of the tilts conducted prior to the three treatment periods. None of the measurements showed a change at a 5% significance level, indicating reproducibility in the tilt procedures conducted on different days. This also indicates that the 3-week interval between recumbency periods allowed recovery from the preceding cardiovascular deconditioning. In the second, third, and fourth columns the F values and levels of significance are shown for each measurement, after each treatment, compared with the measurements of the three pooled pre-treatment tilt table procedures. The significant changes in a number of variables indicate that deconditioning occurred during all three treatment periods. In Table III are presented the mean values for each measurement, thus indicating the magnitude and direction of change. In the fifth column in Table II is presented a summary of the analysis

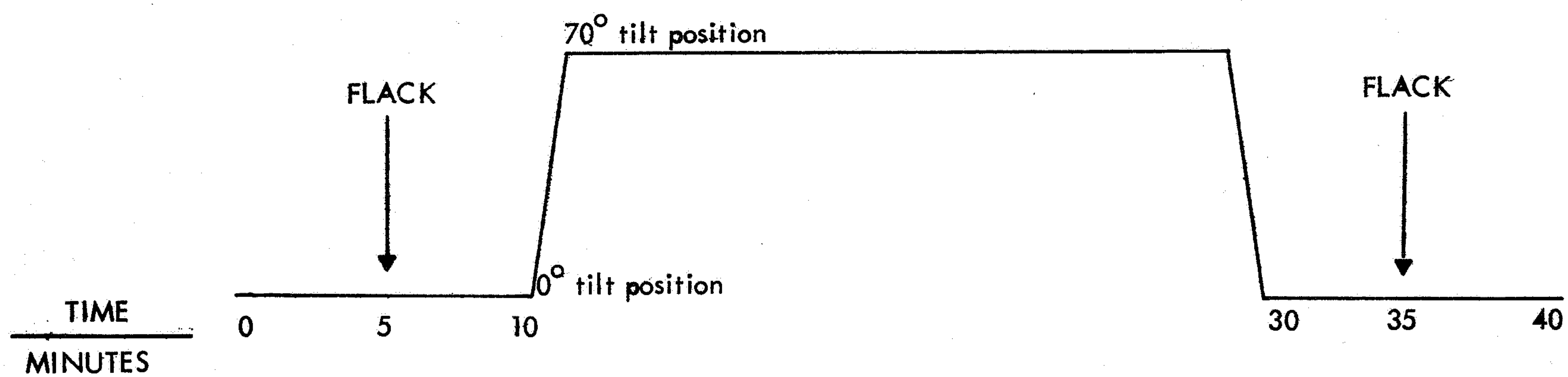

Figure 2. Schematic Diagram of Tilt Procedure

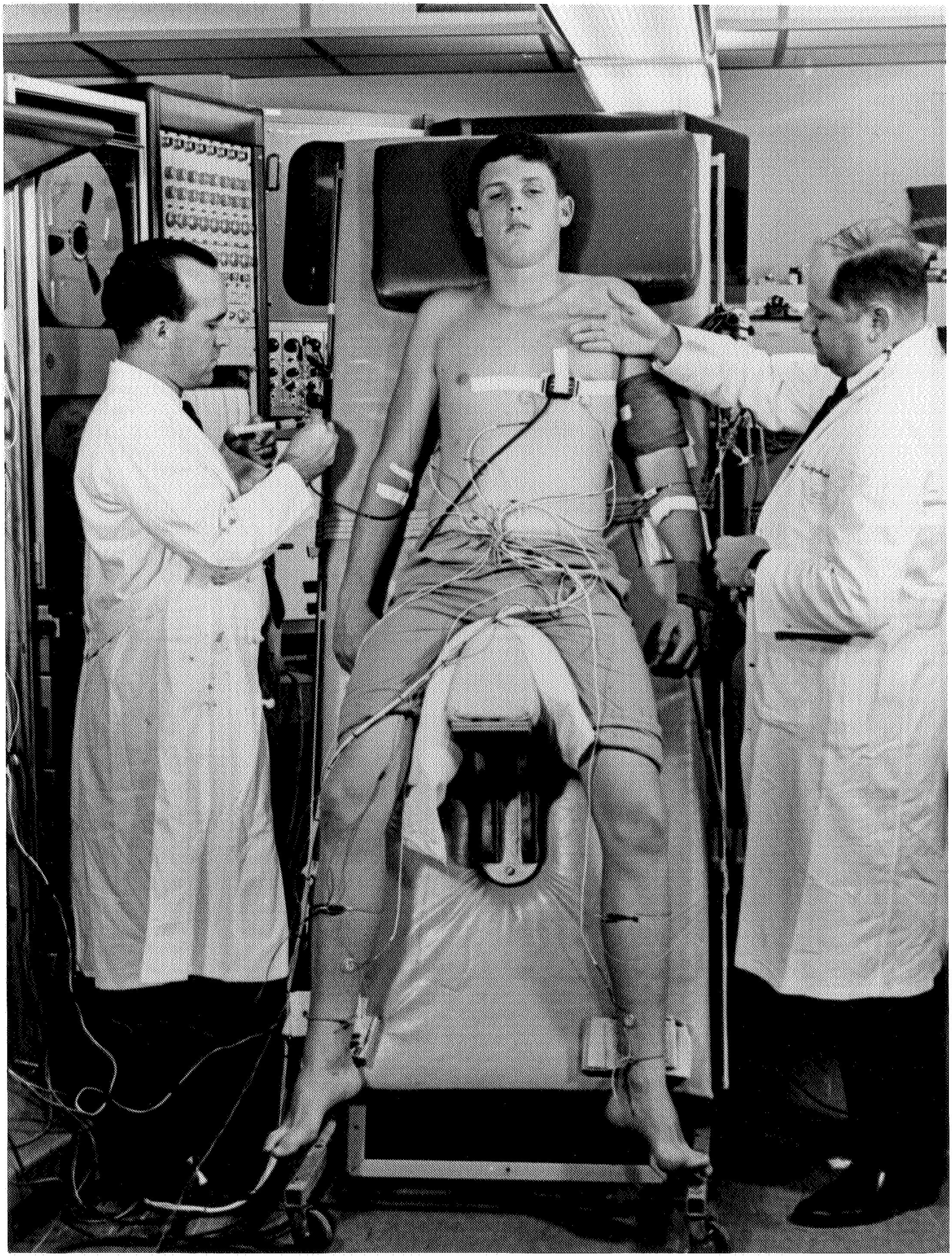

TABLE II

Summary of F Values and Levels of Statistical Significance of Measurements Derived from Tilt Table Procedures

Measurement	Pre Treatment Tilts	Pre vs. Post Bedrest	Pre vs. Post Cuffs	Pre vs. Post Exercise	Post Treatment Tilts
Time to tilt down	2.69NS	1.76NS	8.96**	5.00*	0.85NS
Avg HR pre-tilt	1.50NS	1.46NS	0.81NS	0.04NS	0.34NS
Max HR during tilt	1.46NS	23.29**	9.17**	19.39**	1.30NS
Min HR after tilt	0.46NS	3.65NS	3.98NS	2.01NS	0.03NS
Cng in HR with tilt	1.20NS	22.91**	7.81**	27.65**	2.39NS
Frac incr in HR	1.10NS	18.18**	6.71*	30.03**	1.81NS
Avg pre HR-avg post	0.53NS	1.12NS	0.87NS	4.18*	0.22NS
Time of max HR	0.53NS	0.00NS	3.27NS	0.65NS	1.04NS
Time to 0.8 max	0.50NS	0.14NS	2.54NS	0.93NS	0.67NS
Time to plateau	0.44NS	1.96NS	1.10NS	7.20*	3.38NS
Slope to 0.8 HR	2.49NS	1.20NS	3.74NS	1.52NS	0.17NS
Slope to plateau	0.69NS	9.85**	16.97**	8.67**	0.16NS
Avg PP pre-tilt	0.42NS	3.90NS	2.96NS	0.03NS	0.98NS
Min PP during tilt	0.81NS	0.03NS	4.46*	1.25NS	2.96NS
Avg pre PP-min during	0.56NS	1.66NS	8.45**	1.47NS	2.46NS
Frac decrease in PP	0.76NS	0.61NS	6.26*	1.50NS	2.77NS
Time of min PP	3.43NS	6.88*	0.11NS	0.41NS	4.34*
Avg pre mean-min dur	1.23NS	3.65NS	9.81**	2.48NS	1.29NS
Slope of diastolic BP	1.83NS	0.45NS	7.94**	5.09*	1.07NS
Slope of systolic BP	2.82NS	0.16NS	3.19NS	3.66NS	0.69NS
Slope of mean pressure	2.39NS	0.30NS	5.58*	4.60*	0.92NS
Slope of PP	3.03NS	0.02NS	0.32NS	1.11NS	0.17NS

* $p < 0.05$

** $p < 0.01$

NS Non-significant

TABLE III

Means of Measurements from Tilt Table Data*

Measurement	Pre De-conditioning	Post Bed-rest	Post Bed-rest with Cuffs	Post Bed-rest with Exercise
Time to tilt down	23.9	21.0	17.4	19.0
Avg HR pre-tilt	64.1	66.5	66.1	64.0
Max HR during tilt	97.8	119.7	111.9	119.0
Min HR after tilt	54.7	58.8	58.6	58.1
Cng in HR with tilt	33.7	53.1	45.8	55.0
Frac incr in HR	0.53	0.81	0.71	0.87
Avg pre HR-avg post	6.8	4.6	5.2	3.1
Time of max HR	12.2	11.8	8.0	10.0
Time to 0.8 max	6.4	5.8	3.9	5.0
Time to plateau	3.3	4.1	2.8	5.0
Slope to 0.8 HR	6.5	9.0	10.9	9.6
Slope to plateau	5.2	8.3	9.4	8.9
Avg PP pre-tilt	56.0	61.0	60.0	57.0
Min PP during tilt	31.0	30.0	21.0	26.0
Avg pre PP-min dur	25.0	31.0	39.0	31.0
Frac decr in PP	0.45	0.51	0.65	0.54
Time of min PP	8.4	13.9	7.7	10.0
Avg pre mean-min dur	27.0	41.0	50.0	38.0
Slope of diastolic BP	-1.1	-1.8	-4.7	-3.9
Slope of systolic BP	-2.0	-3.0	-6.4	-6.1
Slope of mean pressure	-1.3	-2.2	-5.3	-4.6
Slope of PP	-0.9	-1.2	-1.8	-2.2

*Units are indicated in text.

of variance which compares the three post-treatment (during bedrest) tilts, indicating no statistically significant difference in the tilt procedures, except for the time to reach minimum pulse pressure.

In Table III are presented the means of measurements for the different conditions. The pre-recumbency tilts were pooled and the post-treatment (during recumbency) tilt mean measurements are presented for each treatment. The units of the various measurements are as follows: pressure (mm. Hg), heart rate (beats/minute), slope of heart rate (beats/minute/minute), and the slope of pressure (mm. Hg/minute). These data are presented to indicate trends of change in the measurements even though there was no statistical difference in the three post-treatment tilt table procedures. The direction of change in measurements after the three potential treatments (during bedrest) is indicative of the changes that characterize the deconditioning of bedrest.

In Table IV are presented the means of measurements obtained during the tilt procedures which compare the response of non-athletes and athletes. There were some differences in the two groups before deconditioning. Both groups showed the same general pattern of changes characterizing deconditioning.

DISCUSSION

The average heart rate pre-tilt showed a small but non-significant increase after the recumbency periods during which treatment measures were used. This failure to observe an increase in heart rate is different from the increased rates observed by others,[5,8,9,10,16,17,18] and may be because of the short period of recumbency. Likewise, there was but a small difference in the resting heart rate of the athletes compared with the non-athletes. However, all subjects were in good physical condition, and the resting heart rates were low for both groups. The non-athlete/athlete distinction had been made initially on the basis of the medical history of participation in physically competitive sports and an active exercise program.

The failure to observe a significant protective effect from use of leg cuffs, as has been found with extremity cuffs used with water immersion,[6,12] could have been a result of the use of different inflation-deflation cycles, use of leg cuffs only, or differences in the mechanism of deconditioning for bedrest and water immersion. Vogt[12] has suggested that the protective effect of cuffs in water immersion studies may occur with arm cuffs only, and Vogt and Johnson[13] have suggested a possible mechanism to account for the changes. Further studies on cuff timing cycles and use of cuffs on arms and legs only during water immersion are needed to define the reason for the differences observed.

The failure to observe a significant protective effect from the periodic exercises could be explained in more than one way. Either the dose may have been inadequate, or physical inactivity may not be the principal factor accounting for the changes observed in the tilt table test. Vallbona and associates[10] have reported a suggestive protective effect from periodic large doses of isometric exercise during 14 days of bed recumbency. Miller, et al.[7] observed no increased benefit from the use of in-bed exercises during 2 weeks of recumbency.

TABLE IV

Table of Means of Measurements from Tilt Table Studies to Compare Non-athletes and Athletes*

Measurement	Non-athlete Pre**	Non-athlete Post**	Athlete Pre**	Athlete Post**
Time to tilt down	23.9	17.6	23.8	21.1
Avg HR pre-tilt	65.0	67.5	63.0	63.1
Max HR during tilt	102.3	119.1	92.2	114.0
Min HR after tilt	56.8	61.7	52.1	54.5
Cng in HR with tilt	37.3	51.7	29.2	50.9
Frac incr in HR	0.50	0.78	0.46	0.82
Avg pre HR-avg post	5.74	3.12	8.12	5.73
Time of max HR	13.3	8.5	10.7	11.8
Time to 0.8 max	6.27	5.53	6.67	4.08
Time to plateau	3.13	4.20	3.50	3.67
Slope to 0.8 HR	7.50	9.08	5.28	10.8
Slope to plateau	5.46	8.16	4.94	9.72
Avg PP pre-tilt	53.6	58.5	58.3	60.0
Min PP during tilt	28.3	22.5	33.5	29.6
Avg pre PP-min dur	25.3	36.0	24.8	30.4
Frac decr in PP	0.47	0.62	0.42	0.50
Time of min PP	8.47	10.02	8.25	11.2
Avg pre mean-min dur	27.7	51.8	25.0	31.9
Slope of diastolic BP	-1.14	-3.71	-0.96	-3.13
Slope of systolic BP	-1.66	-5.95	-2.42	-4.18
Slope of mean pressure	-1.31	-4.46	-1.45	-3.48
Slope of PP	-0.52	-2.24	-1.45	-1.05

*Units are indicated in text.

**All tilts pre are pooled, all tilts post are pooled.

The use of an objective approach in the analysis of tilt table data collected during controlled experimental circumstances provides a significant aid in the interpretation of tilt table data. Such is especially the case where there is a need to detect and interpret changes in tilt table responses that are directly attributable to the procedure or treatment measure, and there is need to distinguish normal variations in response from repeated tilt procedures on a given subject or group of subjects.

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PLASMA VOLUME AND EXTRACELLULAR FLUID VOLUME CHANGE ASSOCIATED WITH 10 DAYS BED RECUMBENCY

by

Fred B. Vogt, M.D.* and Philip C. Johnson, M.D.**

INTRODUCTION

A decrease in plasma volume has been noted to occur during various ground-based deconditioning experiments,[4,5,7,8,9,10,11,12,13,14,15,19,20,21] as well as in association with recent Gemini space flights. Some investigators have speculated that a decrease in plasma volume (PV) is one of the primary mechanisms responsible for the manifestations of tilt table intolerance seen after such deconditioning experiments. Supportive evidence for this hypothesis has resulted from tilt table studies performed after rapid removal of known amounts of blood from individuals,[6] thus eliminating certain components of cardiovascular deconditioning, such as physical inactivity, but at the same time possibly introducing other unknown reflex mechanisms. It also has been speculated that this decline in plasma volume is associated with a corresponding decline in extracellular fluid volume (ECF), especially in the lower portions of the body.[16] The proposed mechanism responsible for the decline in the volume of these spaces involves a physiological adaptation of the body from the condition wherein there are relatively large hydrostatic pressure forces at the capillary level that occur periodically in persons undergoing normal activity, to the condition wherein these forces are removed when there is a lack of gravity acting parallel to the long axis of the body.

It is the purpose of this paper to document the changes in the plasma volume and extracellular fluid compartments, and other related measurements, during three periods of 10 days recumbency in a group of 10 subjects. The experimental design utilizes potential treatment measures which could be used in an actual flight situation. The design does not allow direct correlation between the decline in plasma volume and tilt table intolerance observed in these subjects and as reported elsewhere.[18] This paper is one of a series of reports which describe in detail the changes in various tests performed and measurements made on a group of subjects participating in a complex experimental design.[3,17]

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METHOD

Subjects

Eleven healthy adult young male subjects participated in three periods of 10 days bedrest conducted at the Texas Institute for Rehabilitation and Research in the summer of 1964. Subject characteristics are shown in Table I. Subject A.P.K. participated in the first period of recumbency only, and was replaced by L.F.E. who participated in the remaining two periods of recumbency. Subjects who actively engaged in competitive sports and followed a regular physical training schedule were classified as athletes.

Calendar of Experimentation

The calendar of experimentation is shown in Figure 1. The subjects were divided into two groups for convenience in testing, with one-half of the subjects going into bedrest a day before the other half. Similarly, the first group of subjects was ambulated 1 day earlier than the second group. During the first recumbency period, subjects M.A.C., R.S.H., J.A.H., G.S.R., and B.E.H. had intermittent leg cuff inflation, while the remainder of the subjects underwent a periodic exercise program.[1,2] Finally, during the third period of recumbency, all subjects went through a 10 day period of bedrest without any potentially protective mechanisms.

Experimental Circumstances

The subjects were admitted to the Texas Institute for Rehabilitation and Research as patients for experimental studies. During a 94-day stay at the hospital, they were fed controlled diets containing approximately 8-10 grams salt daily. Fluid intake was allowed ad libitum. In the intervals between bedrest periods, the subjects were maintained on controlled diets and sleep schedules. During the day, they were encouraged to follow activity patterns similar to that followed prior to admission, except for the imposition of food and sleep control. During the periods of recumbency, the subjects were required to maintain a horizontal position in bed. They were allowed one pillow under their heads, were allowed to roll from side to side in bed, and by turning on their sides, were allowed to feed themselves. They were under supervision of a physician at all times during recumbency.

Cuff treatment was provided 24 hours a day during the 10 day period of recumbency, using 3.75 inch wide cuffs applied to the upper part of the thigh, inflated to a pressure of 70-75 mm. Hg. The cuff inflation-deflation cycle was 5-minutes-on, 10-minutes-off, with the cuff inflation phase taking 5 to 8 seconds. Bungie-cord exercises were provided hourly for 10 treatment periods a day starting at 8 a.m. The exercises were performed in the horizontal position by the subject placing his feet in a bracket at one end of the rubber Bungie-cord to provide a fixed point against which to pull. The subject kept his legs partially flexed to provide muscular exercise to the lower as well as the upper extremities. The extent or length of pull attained for each Bungie-cord exerciser was determined for each subject prior to bedrest. For each subject, a

TABLE I

Subject Characteristics

Subject Initials	Hospital Number	Age (yrs.)	Weight* (kg.)	Height* (cm.)	BSA** (m^2)	Occupation
M.A.C.	70020	23	65.3	178	1.81	Student (NA)
L.F.E.****	70028	24	74.3	188	2.00	Student (A)
R.S.H.	70021	22	65.2	172	1.77	Student (A)
J.A.H.	70022	23	81.1	179	2.01	Student (NA)
B.E.H.	70019	21	69.8	178	1.88	Student (NA)
A.C.I.	70018	22	51.0	163	1.52	Student (A)
A.P.K.***	70023	24	59.4	174	1.72	Student (NA)
W.F.M.	70024	23	66.4	171	1.78	Student (NA)
C.E.R.	70025	25	80.6	192	2.11	Student (A)
G.S.R.	70026	26	65.6	178	1.83	Student (A)
R.R.T.	70027	22	78.2	172	1.92	Student (NA)

A Athlete
NA Non-athlete
* At the beginning of the experiment
** Dubois Body Surface Chart (prepared by Boothby and Sandiford)
*** Participated in the first period of bedrest only
**** Participated in the second and third periods of bedrest only

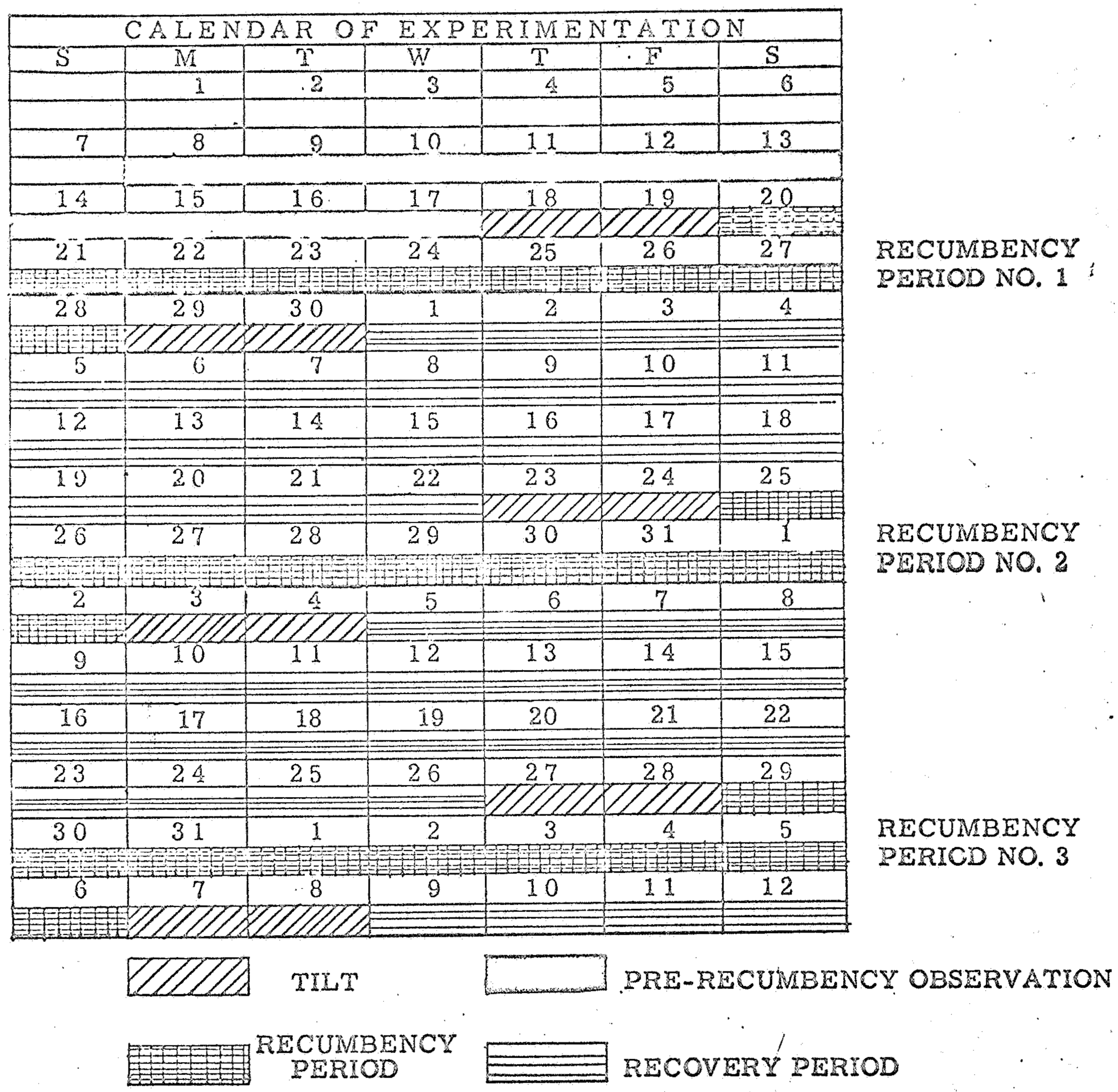


Figure 1. Calendar of Experimentation

work load was determined which produced a moderate cardioacceleration in response to the exercise, which consisted of 120 pulls on a prescribed exerciser at a rate of one pull per second.

Body compartment measurements were performed periodically during the 94-day experiment using a multiple isotope dilution technique*. Primary attention was directed at evaluation of plasma volume and extracellular fluid volume changes, although periodic red cell mass and total body water determinations were done as described below. A Packard Autogamma System was utilized for determination of iodine (I^{131} and I^{125}) and chromium (Cr^{51}). A Packard Tricarb system was utilized for determination of sulfate (S^{35}) and tritium (T^{3}).

Tests Performed

Plasma volume was determined using iodinated human serum albumin (IHSA), allowing a mixing time of 10 minutes. Measurements were made in the control period prior to and after recumbency, on the first day of recumbency (after the subject had been horizontal for approximately 12 hours) and on days 4 and 10 during the recumbency period. Determinations made during the ambulatory periods were obtained within 2 hours of the time the subjects arose after a night's sleep. Duplicate 1 ml. samples of plasma were counted on the Packard Autogamma. Injected doses of the IHSA were increased during the course of the experiment, as required to obtain valid results considering injections of isotope from previous tests.

Extracellular fluid volume was determined by using the sodium sulfate (S^{35}) dilution technique. Venous blood samples were withdrawn at 60, 120, 150, and 180 minutes after injection of the isotope for construction of a dilution curve used in calculating the extracellular fluid volume.

Red blood cell mass was determined several times prior to the first period of recumbency by a technique using sodium chromate (Cr^{51}) tagged red blood cells. A 10 minute mixing period was allowed after injection of the tagged cells before the determination. These pre-recumbency tests served as baseline determinations for comparisons to a single red cell mass determination made after the second period of recumbency. More frequent measurements of red cell mass were not made because of the isotope dose exposure required in these extensive studies performed repeatedly on the same subjects.

Total body water (TBW) determinations, utilizing a tritiated water dilution technique, were done on day 1, 4, and 10 of recumbency periods 1 and 3, as well as several times prior to recumbency period 1, and once in the interim between periods 2 and 3. More frequent measurements were not made because of the cumulative dose of isotope which would have been required to obtain technically acceptable results. Venous blood samples were withdrawn at 60, 120, 150 and 180 minutes after injection of the radioactive water dose to determine the dilution curve for calculation of the total body water volume.

*The detailed technique is available upon request from the authors.

Hematocrits (Hct.) were determined using a microcapillary technique and centrifuging the venous blood for 5 minutes. Prior to breakfast, and after urination, body weights were determined on a platform scale which could be read to $\pm$ 50 grams. Circumference measurements were made daily at three sites on each leg during the course of the study; changes in calf circumference were measured during tilt procedures using a mercury-in-rubber strain gauge apparatus.

Date Analysis

Data were analyzed using a Least Squares Analysis of Variance technique. The results presented here refer to the nine subjects who participated in all three periods of recumbency. The analysis of variance technique utilized the three main effects (a) treatment, (b) day, and (c) athlete/non-athlete subject classification, with use of interactions between the three to arrive at the residual term for calculating the F values presented in the tables. In Table II is shown an example of a computer print-out of the analysis of variance performed, with a print-out of a table of means tabulated below the results of the analysis of variance. For simplicity of discussion, the data collected on days 1, 4, and 10 of bedrest are considered in more detail than other data collected during the control periods.

RESULTS

In Table III is presented an over-all summary of F values for the analysis of variance performed on the measurements obtained for plasma volumes, hematocrit, total body water, and extracellular fluid. Since there was no statistical significance (at $p = 0.05$) in the analysis of variance for the main effect treatment, the results of the treatments of bedrest, bedrest with cuffs, and bedrest with exercise will be discussed as representing statistically the same experimental condition, describing primarily the effects from recumbency. There are noted in Table III highly significant differences in athlete and non-athlete for the measurements plasma volume and hematocrit. An analysis of variance performed using the main effect, day of treatment, indicates significant changes in plasma volume, hematocrit, and extracellular fluid volume. Interaction between the main effects were statistically non-significant in this experiment.

In Table IV are summarized the means for the three treatment periods of the measurements made on days 1, 4, and 10. The following figures display the means obtained for the various measurements on different treatment days. In Figure 2 is shown the average plasma volume change by day for the three periods of recumbency. In Figure 3 are shown the corresponding hematocrit changes for the same day, indicating the inverse relationship between these two measurements. The average extracellular fluid volume changes by day for the bedrest periods combined are shown in Figure 4, indicating a continuous trend downward in this measurement. In Figure 5 the average total body water volumes by day for periods 1 and 3 combined are presented.

In Table V are presented the data for comparison of the individual subjects, with distinction made between athletes and non-athletes, of the measurements (a) total body water, (b) extracellular fluid, and (c) plasma volume. The values presented are the means of measurements made in the control periods, and the percentage of body weight represented by each of these means. There is evident a higher percentage of water content in all body compartments for the subjects classified as athletes.

TABLE II

Sample Analysis of Variance Performed on Data

Day (1, 4, 10)	Analysis of Variance			E.C.F.
	DF	SS	MS	F
Total	80.	0.497222900E 03		
Athlete/Non-athlete	1.	0.180500799E 02	0.180500799E 02	3.0578
Treatment	2.	0.330019508E 01	0.165009756E 01	0.2795
Day	2.	0.656642903E 02	0.328321454E 02	5.5620
Interaction	2.	0.700192451E 01	0.350096226E 01	0.5931
Interaction	2.	0.727037741E 01	0.363518870E 01	0.0062
Interaction	4.	0.736740553E 01	0.184185135E 01	0.3120
Residual	67.	0.395495360E 03	0.590291583E 01	

Table of Means for Main Effects

Athlete/Non-athlete	14.6611	15.6111	
Sample Size	36	45	
Treatment	15.4296	15.0667	15.0704
Sample Size	27	27	27
Day	16.3000	15.1926	14.0741
Sample Size	27	27	27

TABLE III

Over-all Summary of F Values

Subject	Day	Ath./Non-ath.	Treatment	Day
P. V.	1, 4, 10	4.89*	1.15	7.17**
H. C. T.	1, 4, 10	41.30**	2.35	32.31**
T. B. W.	1, 4, 10	0.35	0.89	0.45
E. C. F.	1, 4, 10	3.06	0.28	5.56**
P. V.	1, 4	4.80*	1.70	8.21**
H. C. T.	1, 4	24.06**	0.97	45.05**
T. B. W.	1, 4	0.56	0.00	0.10
E. C. F.	1, 4	1.89	0.22	2.43

* $p < 0.05$

** $p < 0.01$

TABLE IV

Average Values for Bedrest Days for Three Treatment Periods Combined

Measurement	Day 1	Day 4	Day 10
Plasma Volume (liters)	3387	3055	2963
Hematocrit (%)	41.1	45.0	44.3
Total Body Water (liters)	45.8	45.1	45.1
Extracellular Fluid (liters)	16.3	15.2	14.1

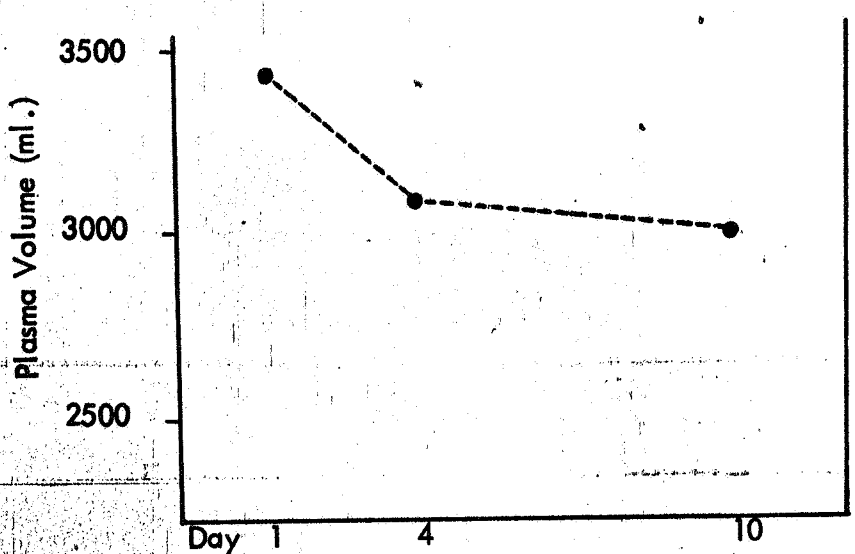


Figure 2.

Average Plasma Volumes for Bedrest Days of Three Treatment Periods Combined

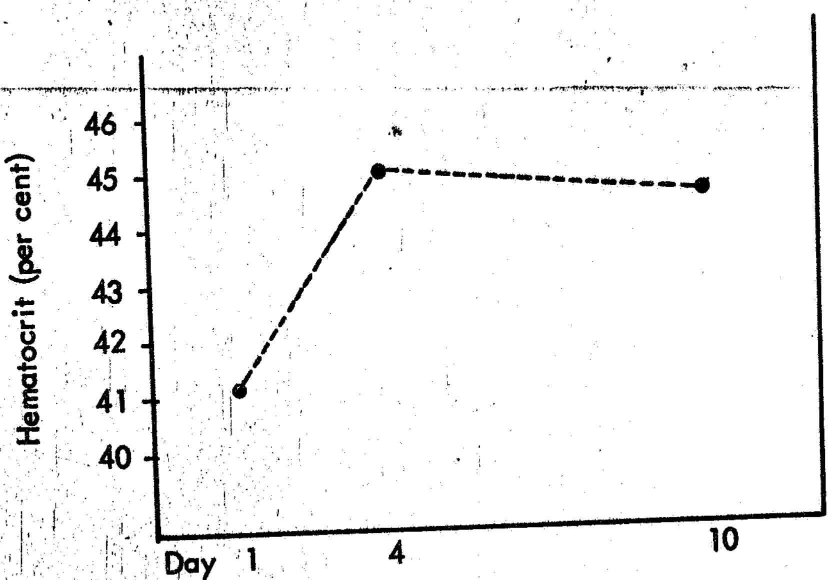


Figure 3.

Average Hematocrit for Bedrest Days of Three Treatment Periods Combined

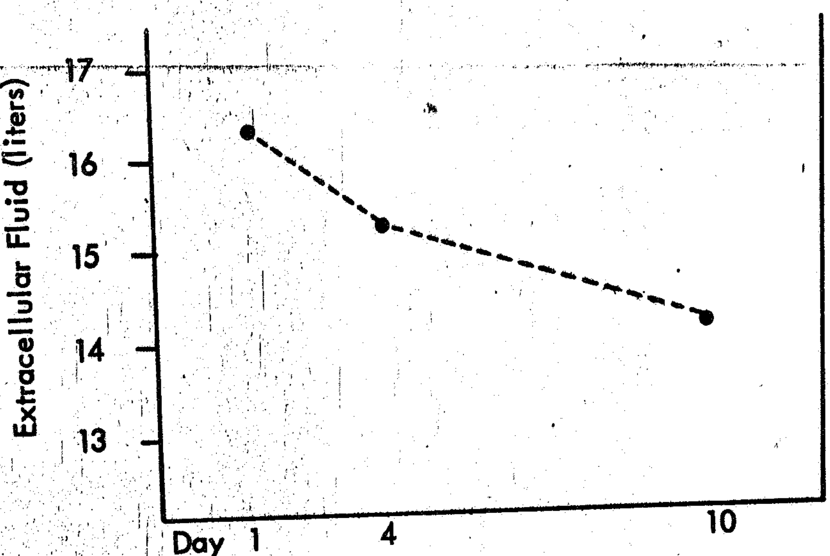
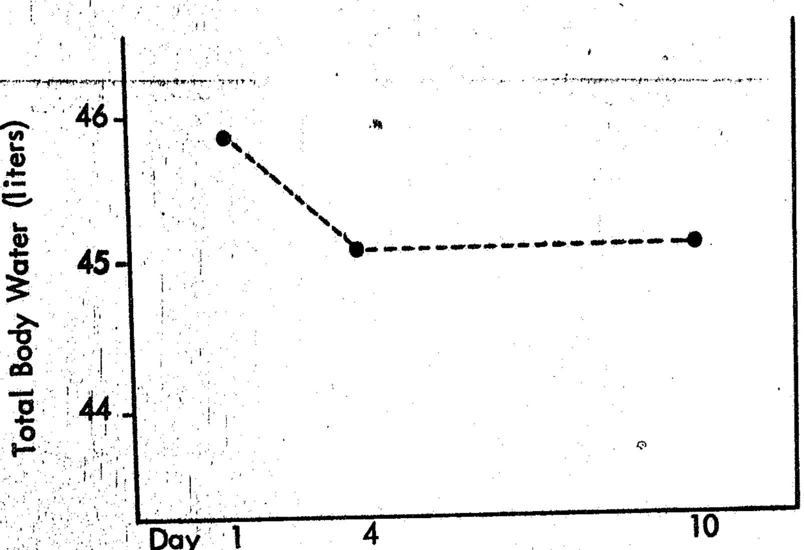


Figure 4.

Average Extracellular Fluid for Bedrest Days of the Three Treatments Combined



*No analyses performed in Period 2

Figure 5.

Average Total Body Water for Bedrest Days of Periods 1 and 3 Combined*

TABLE V

Body Compartment Comparisons for Athletes and Non-athletes

Subject Initials	Body Weight (kg.)	TBW (liters)	TBW (%BW)	ECF (liters)	ECF (%BW)	PV (ml.)	PV (%BW)
B.E.H.	69.8	42.8	61.3	16.0	22.9	3123	4.5
M.A.C.	65.3	39.6	60.6	16.8	25.9	3283	5.0
R.S.H.*	65.2	41.1	63.0	15.6	23.9	3381	5.2
A.P.K.	59.4	37.2	62.6	14.5	24.4	3583	6.0
G.S.R.*	65.6	40.7	62.0	16.6	25.3	3712	5.7
A.C.I.*	51.0	32.5	63.7	12.5	25.5	2660	5.2
W.F.M.	66.4	37.3	56.2	14.9	22.4	2998	4.5
J.A.H.	81.1	44.2	54.5	18.5	22.8	3256	4.0
R.R.T.	78.2	41.8	53.4	17.5	22.2	3620	4.7
C.E.R.*	80.6	48.8	60.5	18.2	22.6	4253	5.3
L.F.E.*	74.3	50.4	67.6	19.3	25.8	3761	5.1

*Athletes

There was an average decline in red cell mass of 215 ml., comparing the pre-recumbency value of 2265 ml. for the nine subjects with the 2050 ml. value obtained midway between the second and third periods of recumbency. There was a variable change in body weight after the periods of recumbency, with small increase or decrease in different subjects; no consistent pattern of weight change was observed.

Leg circumference changes, measured at the calf, showed a small decrease during the periods of recumbency, with no increase in circumference noted in the subjects when cuff treatment was in operation. There was not a definite relationship during tilt table studies of rate of change in leg circumference, or total change in leg circumference, to the occurrence or non-occurrence of syncope; no definite pattern of change of leg circumference was noted to distinguish the pre and post-recumbency tilt procedures. No definite correlation could be established with tilt intolerance and the amount of decrease in plasma volume.

DISCUSSION

The observation of no statistically significant differences in the group response for the treatments used in this experiment does not necessarily mean that no effect results from the treatments; more exercise or different cuff timing cycles may have produced significantly different results. Treatment measures were devised and tested experimentally using an experimental design that could be applied to a space flight situation.

The rapid decline in plasma volume showed a stabilization in volume between days 4 and 10. Some studies[4,20] provide evidence that this decline reverses as the deconditioning period progresses, while other investigators[12,14] have noted large changes in plasma volume or blood volume associated with prolonged recumbency. Other work conducted by the authors in similarly controlled experimental circumstances would support the first observation.[19] Observation of tilt table intolerance after prolonged recumbency, with corresponding return of blood volume to normal values,[19] suggests that although a decrease in plasma volume could be one factor responsible for tilt table intolerance, it is not the only mechanism operating to produce the effect. From the authors' observations, it might be concluded that under controlled experimental circumstances, it is likely that vascular volume compensatory mechanisms will result in a restoration of "normal" blood volumes as the experiment progresses.

In contrast, the data from this study indicate a progressive decline in extracellular fluid volume. No further data are available to predict whether or not this decline is likely to progress for a longer period of time. This decline in extracellular fluid volume could be a contributing mechanism to the tilt intolerance seen after deconditioning, if there results an increased transudation of fluid from the vascular to extravascular space when the subject is exposed to gravity vectors acting parallel to the axis of his body during the tilt procedure after deconditioning.

The failure to observe statistically significant changes in total body water is accompanied by failure to observe weight changes of the subjects. The sensitivity of the method to determine total body water may not be great enough to detect the changes which could be expected under these experimental circumstances. No further interpretation of these measurements is thought justified from the present experimental design.

The decline in red cell mass is probably a real accompaniment of the experimental procedure (bedrest), although repeated removal of blood for laboratory tests must be considered as potentially affecting this measure, especially in view of the small change observed in red cell mass. The exact relationship of the measurement to the periods of recumbency cannot be ascertained, as values were obtained prior to recumbency and between the second and third periods.

The use of the day 1 value as the control value for the measurement was selected by the authors because the subjects had been in bed only 12 hours, which would correspond closely to performing measurements on subjects early in the morning on other so-called controlled days. These measurements were not significantly different from the pre-recumbency measurements and those obtained on day 1 of the first period after 12 hours recumbency. There could be a small bias toward an increased plasma volume after short periods of recumbency, as has been described for certain patients,[22] but which the authors have not documented in normal subjects after 12 hours recumbency.

These data, collected under controlled experimental circumstances, show the reproducibility of the technique and the apparent validity of the methodology for studies of this type. Further documentation of the transitory or progressive changes in the observed measurements must be made before they can be related to tilt table tests as mechanisms of tilt intolerance or simply as occurring incidentally because of the temporal relation of the test procedures.

ACKNOWLEDGMENTS

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THE EFFECT OF EXTREMITY CUFF-TOURNIQUETS ON TILT TABLE INTOLERANCE AFTER WATER IMMERSION

Studies have been conducted that demonstrate cardiovascular deconditioning occurs with prolonged bedrest,[20, 8, 30, 21, 5, 25, 22, 29, 6, 18] water immersion,[10, 14, 15, 11, 12, 2, 17] chair rest,[16] or space flight.[4, 7] The physiological changes that occur in these experimental conditions which are responsible for the increase in heart rate, decrease in blood pressure, and signs or symptoms of syncope during tilt table tests are not understood clearly. The lack of knowledge on the mechanism of deterioration of the cardiovascular system thus has made research on preventive and control measures difficult.

Anti-gravity suits have been found beneficial[18, 19] in preventing orthostatic cardiovascular intolerance in patients, as well as normal subjects deconditioned by either bedrest or water immersion. Periodic rocking beds[30] in a gravity environment have been reported to produce some protective effect from the deconditioning associated with bedrest. Intermittent occlusive venous cuffs have been reported[10] to prevent the occurrence of tilt intolerance after water immersion. The purpose of the work reported in this paper was to reproduce some of the observations made in the water immersion experiment[10] in which cuffs provided a protective effect.

METHODS

Four healthy adult male college students in the age range 21 to 25 years who had participated previously in extensive bedrest studies[24] were used as subjects. Table I summarizes the subject characteristics.

The subjects underwent two six hour periods of water immersion, preceeded and followed by a tilt table test. During the periods of water immersion, the subjects were dressed in bathing trunks and were immersed in a head-out position. They were allowed a minimal amount of activity in the pool, but most of the time remained in a sitting position. Accessory breathing apparatus was not used. The temperature of the water was maintained at approximately 93°F., throughout the periods of immersion.

The day following test number one, the subjects underwent a second period of immersion, test number two, during which they had cuff-tourniquets applied to all four extremities. The cuffs were 3-3/4 inches wide, and were held in place by a velcro material. Because of the posture the subjects maintained during immersion, the cuffs on the lower extremities were located approximately 60-70 centimeters beneath the surface of the water. The cuffs were inflated from a pressure bottle air source to a pressure of 60 millimeters of mercury, with a one-minute-on, one-minute-off time cycle, and had an inflate and deflate period of approximately five seconds. Cuffs on all subjects were inflated simultaneously.

TABLE I.

SUBJECT CHARACTERISTICS

Subject Initial	Age (years)	Weight (kg.)	Height (cm.)	B. S. A. * (m^2)	Occupation
C. E. R.	25	84.4	192.4	2.15	Student Athlete
R. S. H.	22	66.5	172.4	1.80	Student Athlete
W. F. M.	23	67.5	171.0	1.81	Dental Student
B. E. H.	21	70.2	177.8	1.88	Student

* From Dubois Body Surface Chart by Boothby and Sandiford

A tilt table test was performed before and after the water immersion periods using a tilt table with an English saddle type of support described elsewhere.[26] The tilt table was motorized and tilted from horizontal to 70° in thirty seconds. With syncope, or impending syncope, the gear mechanism of the table was disengaged and the subject was tilted down immediately. The subject was transported from the immersion tank to the tilt table test area by means of a stretcher and immediately went into the tilt table test.

The electrocardiogram, impedance pneumogram, cuff-microphone blood pressure, and leg circumference changes were measured during the tilt test using an instrumentation system described elsewhere.[28] The impedance pneumogram and electrocardiogram were taken from electrodes placed across the thorax in the fifth or sixth intercostal space. Indirect blood pressure apparatus[9] was attached to the right arm with a crystal microphone located over the brachial artery; the cuff was operated in 30 second cycles. Leg circumference measurements were made using a Whitney[31] mercury-in-rubber strain gauge apparatus applied to the calf of each leg. A five minute baseline recording was obtained prior to a 20 minute tilt to the 70° position. A five minute period of recording then was obtained after return of the subject to the horizontal position.

The subjects were immersed from 13:00 to 19:00 o'clock to correspond to a urine collection period that was used for a previous 90 day study[24] on this group of subjects. During the periods of immersion, intake and output were recorded carefully. Weights were obtained prior to and after immersion. The subjects were allowed to drink fluid ad libitum. They were fed after the tilt procedure which immediately preceeded the immersion period, and this intake was included as part of their over-all intake. A malted milk was given to them after approximately four hours of immersion.

RESULTS

All four subjects showed a normal response to the control tilt prior to water immersion which was comparable with the responses observed in extensive tilt studies performed on them previously over a period of several months. There was noted an increase in heart rate and a slight rise in the diastolic blood pressure and a slight decrease in the systolic blood pressure, with a distinct narrowing of pulse pressure. There was no definite downward trend of systolic or diastolic blood pressure. There were no signs or symptoms of impending syncope during the control tilt table procedure.

Three of the four subjects showed syncopal reactions following the first six hour period of water immersion. Figure 1 summarizes the duration of tilt procedure by bar graphs. The change from a pre-tilt five minute average heart rate to the maximum one minute average heart rate during tilt for the subjects is shown by a darkened bar line in the center of the bar representing duration of tilting. The third subject, C. E. R., did not show syncope, but did demonstrate a significant rise in heart rate in his first post-immersion tilt test.

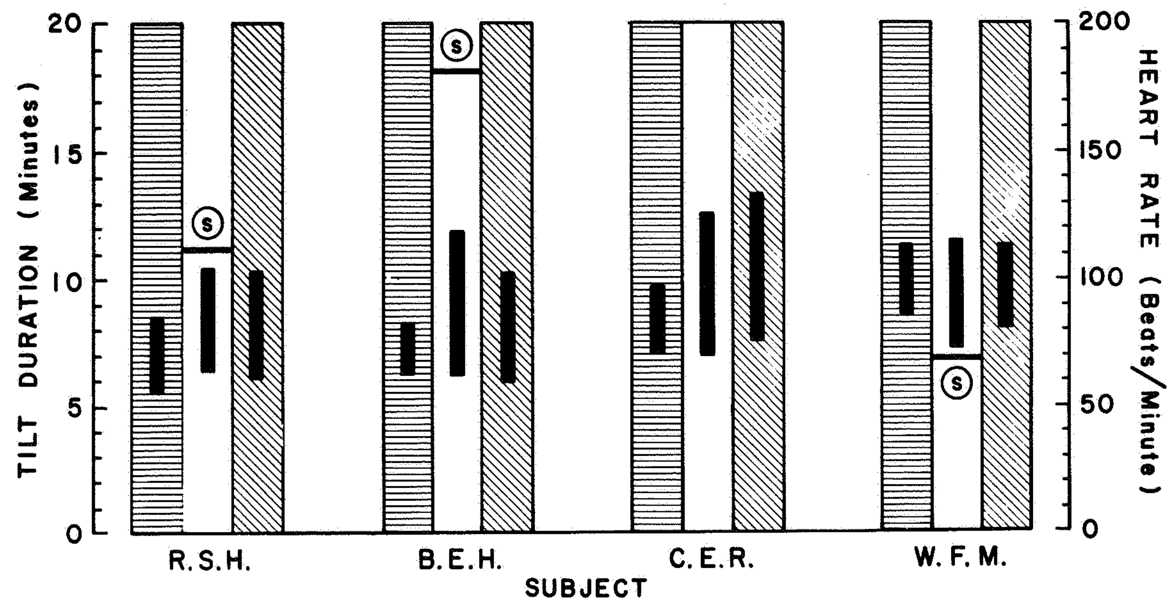

Figure 1. Summary of tilt characteristics for water immersion subjects.

The height of the first bar for each subject represents the tilt duration for the control tilt; the height of the second bar represents the tilt duration for the tilt following 6 hours of water immersion; and the height of the third bar represents the tilt duration for the water immersion experiment to which extremity cuffs were added. The occurrence of syncope is represented by S. The solid lines in the bar graphs represent the change in heart rate from a pre-tilt five minute average to the maximum one minute average in the 70° position.

During the tilt test following the second water immersion period, to which a cuff-tourniquet treatment had been added, none of the four subjects experienced syncope. There was, however, still evidence of an increase in heart rate with tilting compared to control values, although the change in heart rate was not as great as after the first test.

Figures 2, 3, 4, and 5 show the tilt table data in graphic form for each individual to allow ready comparison of the responses for the various test circumstances. Dashed lines represent control values and solid lines the post-immersion values. Five minutes of control data is presented prior to tilting to 70^{o} and five minutes of recovery data is presented after tilt down.

Subject weights did not change significantly during the immersion periods and the minor changes are accounted for by the intake-output differences during the test. None of the subjects complained of excessive thirst at any time. Table II presents the change in body weight, oral intake, and urine output data obtained during the two tests. There appeared to be some difference in the volume outputs for the two immersion periods, but the urine specific gravity did not change significantly during the period of immersion. Total urine volumes were somewhat higher than the average volume outputs for corresponding timed periods of collection in studies performed previously on the subjects, but the range in day-to-day variation in these earlier studies is large enough to make it impossible to say that a significant diuresis existed during this water immersion study.

Leg calf measurements made in the recumbent position on the tilt table prior to tilt did not show significant changes post-immersion compared to pre-immersion. Calf circumference changes during tilt ranged from 3 to 5% during the twenty minute tilt, but there was no good correlation of this with the degree of tilt table intolerance observed.

DISCUSSION

The mechanism of the protective effect of the cuff-tourniquets suggested in Graveline's experiment[10] and reproduced to some extent in this study is not clear. Interpretation of the effects becomes difficult because of the many complicating factors that result from placing a person in a warm and wet environment, and one which provides pressure forces that act upon the body cavities in a poorly understood manner. Of significance, however, is that the tilt table intolerance does occur with water immersion in as relatively a short time span as has been found in space flights, and that it is prevented under experimental conditions identical to that which produces the deconditioning except for the addition of extremity cuff-tourniquets. Of even more significance is that this type of treatment or preventive technique offers itself to application to space flight situations since its mechanism of operation does not depend on a gravity environment. However, the likelihood of protection from cardiovascular deconditioning

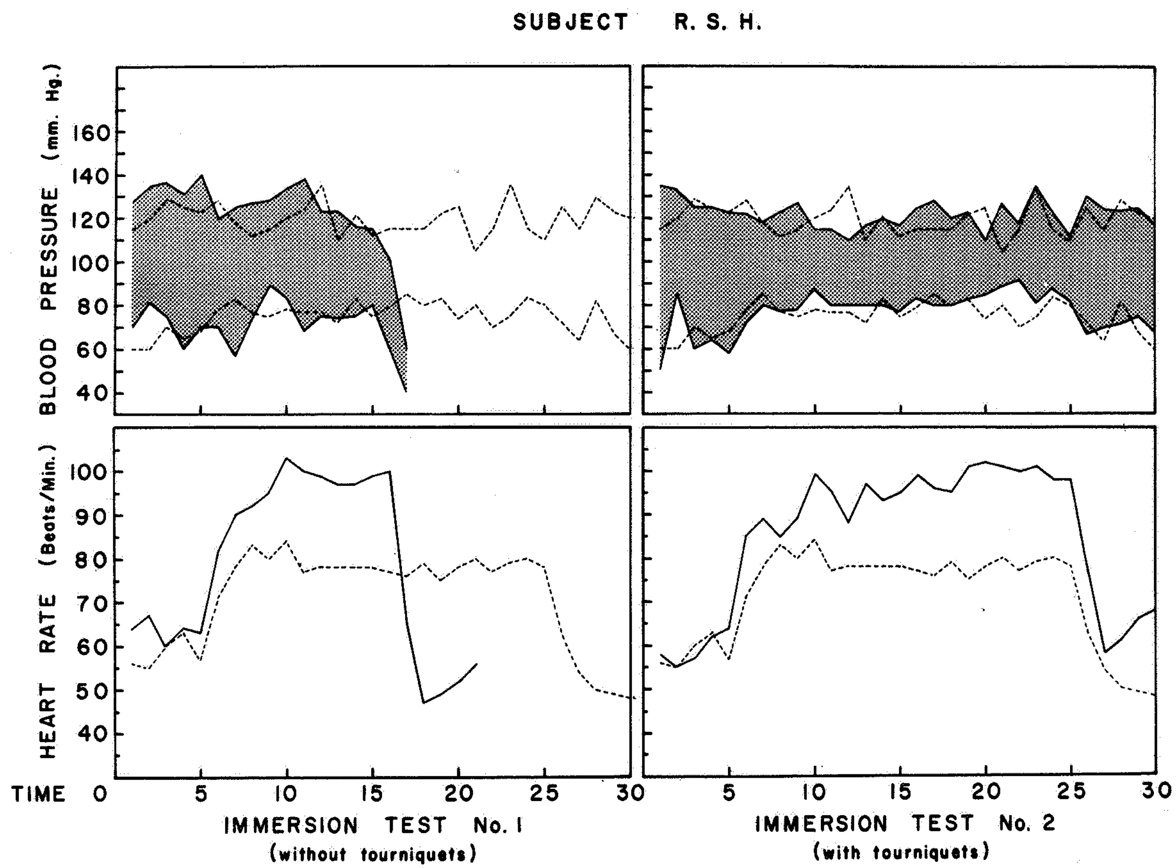

Figure 2. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

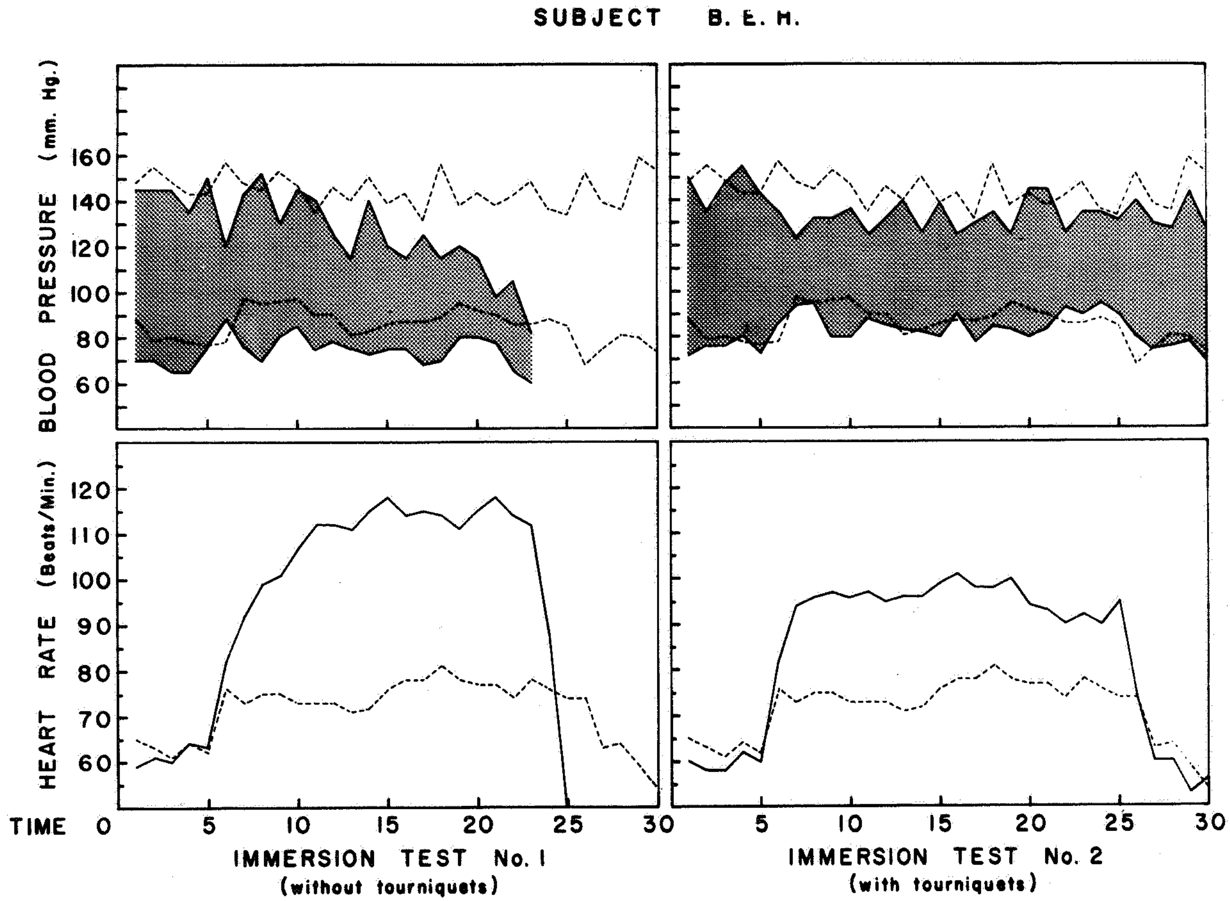

Figure 3. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show restults of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

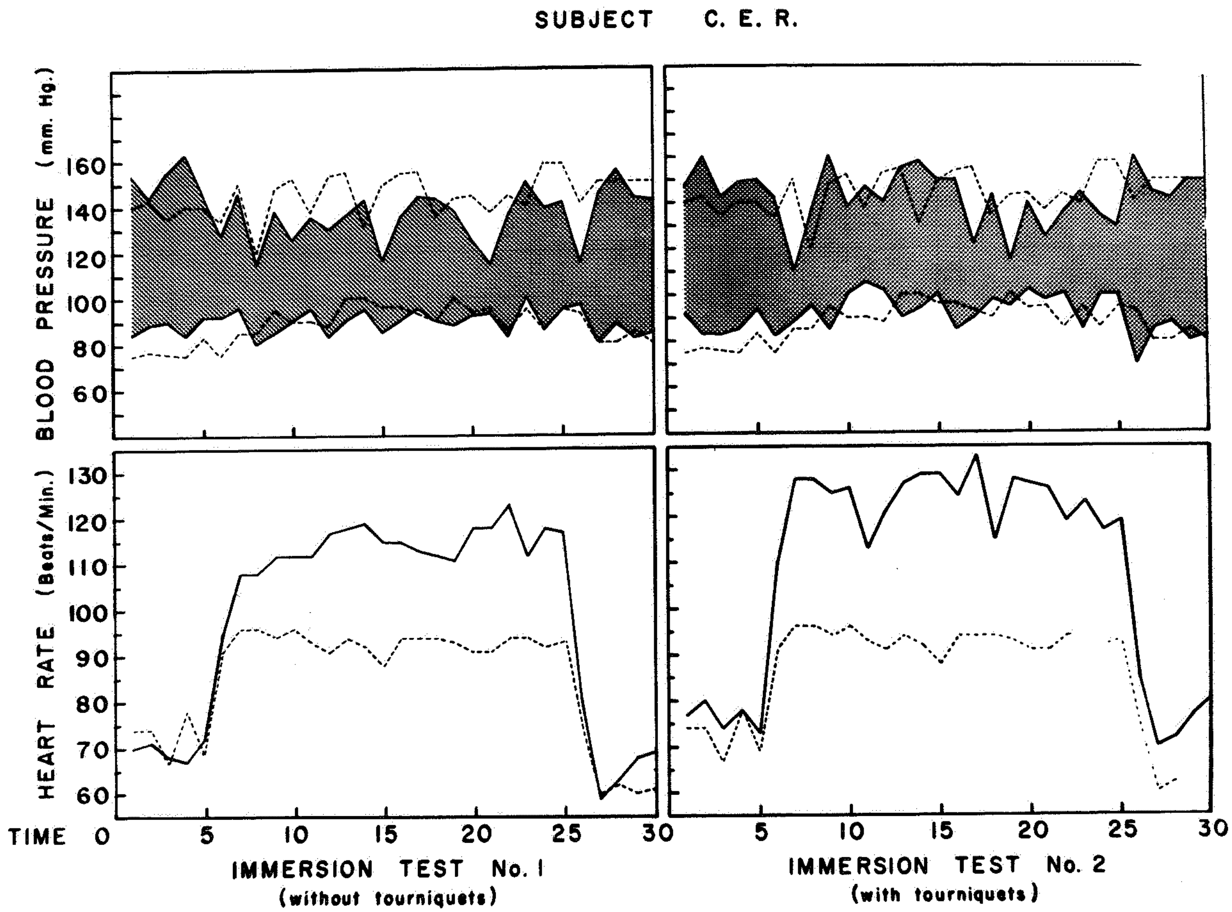

Figure 4. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

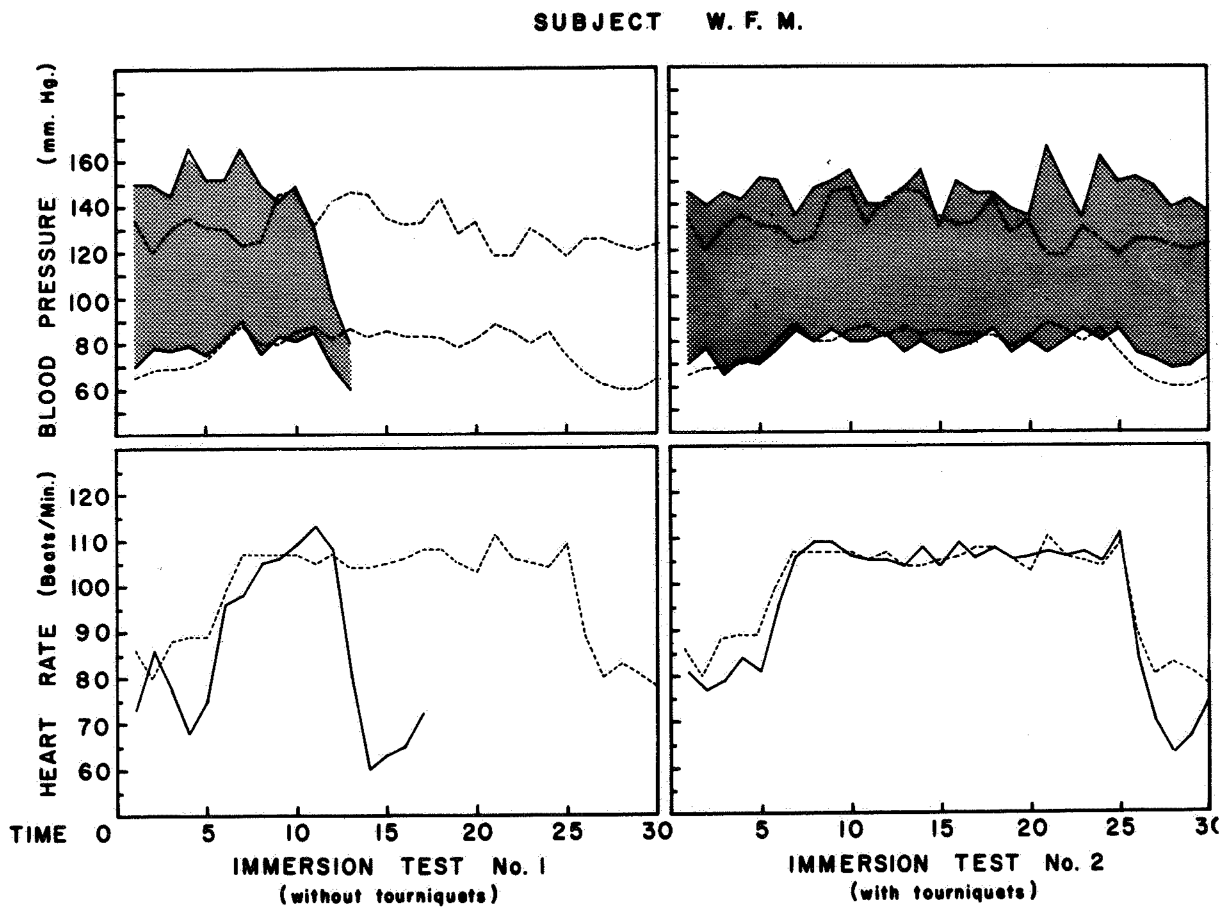

Figure 5. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

TABLE II.

ORAL INTAKE - URINE OUTPUT DURING WATER IMMERSION

		Test No. 1			Test No. 2		
Subject	Control (ml.)*	Intake (ml.)	Output (ml.)	Weight Change (kg.)	Intake (ml.)	Output (ml.)	Weight Change (kg.)
C. E. R.	200 290 560	1200	900	-0.2	1160	530	+0.3
R. S. H.	220 295 385	800	510	-0.1	1500	190	+0.9
W. F. M.	270 500 770	800	390	-0.2	1300	360	+0.6
B. E. H.	195 412 770	1000	760	0.0	1500	620	+0.3

* One week control on each subject during normal activity, giving average urine volumes with minimum and maximum values for these periods above and below the average value.

of space flight by a similar cuff-tourniquet technique would likely depend on a common mechanism of production to that found with water immersion. A possible mechanism to explain some of the factors responsible for the tilt table intolerance seen after water immersion is discussed elsewhere[27] in observations made on the same group of subjects who participated in the study reported herein.

The use of subjects in this experiment who have had considerable experience with tilt test procedures lessens the likelihood of any sporadic subject responses because of extreme anxiety or uncertainties of experimental procedures on the part of the subjects. Further, since the two experiments were performed in close time relationship, any bias due to lack of reconditioning of the subjects would be against reproducing the findings of Graveline.[10]

Diuretic responses have been known to occur with prolonged water immersion. Bazett[1] noted this diuresis as early as 1924 and numerous other observers,[14, 11, 12, 2, 13] have confirmed it. One group,[3] however, did not report a diuresis with water immersion. The failure to observe a significant diuresis in this study raises further questions as to the meaning of diuresis observed by others. But, the failure to observe a marked diuresis and intense thirst, while at the same time observing considerable signs of cardiovascular deconditioning points to this diuresis being a less significant contributing factor to the tilt intolerance. Consideration must be given to the fact that these subjects previously had undergone many test procedures in the experimental laboratory. Anxiety in an inexperienced subject could result in a chain-reaction of increased-intake, increased-output to explain some of the observations in other studies. It is also possible that this group of subjects may have experienced a diuretic response if they had been immersed for a longer period of time. A more detailed account of the fluid-electrolyte and plasma volume responses found in this experiment is in progress and will be reported at a near date.[27]

Cardiovascular deconditioning is spoken of in terms of the orthostatic increase in heart rate, drop in blood pressure, and signs and symptoms of impending or actual syncope. From the experience of the author, it would seem that the order of severity of tilt intolerance after prolonged bedrest is reflected first in heart rate changes, next by narrowing of pulse pressure with a trend downward in blood pressure, with systolic pressure falling more predominantly until the presyncopal condition presents, and then finally, syncope. It has been noted[23] that in the final minutes before syncope, the beat-by-beat variation in heart rate became minimized and the heart rate decreased at the same time that the blood pressure decreased. This parallel drop of heart rate and blood pressure is different from the out-of-phase relationship seen when the subject compensates to the upright position. The responses to tilting after water immersion seem comparable to those observed after bedrest, although they may be produced by much shorter exposure to the experimental deconditioning test.

A point that deserves more consideration in evaluating the protective effect of cuff-tourniquets in this experiment is raised because of counteracting effects produced because of varying depths of the cuffs below water level. In this experiment, a 60 millimeter mercury pressure referenced to the atmosphere was applied to all cuffs. The effect of this pressure in producing additional constriction to the lower extremities above that resulting from the weight of the water itself is the force difference of the pressure applied to the cuff and the pressure force produced by the weight of the water. The implication in this experiment is that perhaps more of the "treatment effect" resulted from the cuffs on the upper extremities.

The simplicity of this experiment and the complexity of the changes in physiological mechanisms with water immersion raise as many questions as are answered. Still, there has been shown to be some protective effect from the use of the cuff-tourniquets. The continued observance of marked changes in heart rate after immersion when cuffs are used indicates that only a first step has been made in the control of the tilt table intolerance after water immersion. Further, there is still not evidence that the cardiovascular deconditioning of water immersion is the same as that found with bedrest studies or in association with orbital flight. Strong considerations and considerable emphasis should be placed on developing "control mechanisms" to protect against the hazardous effects of cardiovascular deconditioning of space flight until more is known of the true meaning of the deconditioning and adequate "preventive measures" can be developed. Continued intensive and cooperative efforts of all investigators in these research areas must be directed to meeting both of these requirements if we are to meet our responsibilities of not only studying the effect of space on man, but in protecting him from these effects.

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A STUDY OF THE EFFECT OF WATER IMMERSION ON HEALTHY ADULT MALE SUBJECTS PLASMA VOLUME AND FLUID-ELECTROLYTE CHANGES

The total effect of prolonged periods of weightlessness on various body functions is not known. There have been observations of orthostatic cardiovascular instability and dehydration in association with two relatively short duration orbital flights of the United States.[3, 6]

Since water immersion and bedrest immobilization experiments are believed to simulate some of the conditions of weightlessness, information from such studies may be helpful to predict cardiovascular changes which may occur in association with future space flights, as well as to help interpret some of the observations made in association with an actual space flight. During water immersion[13, 9, 10, 1, 8, 19, 18, 23] and bedrest[7, 27, 21, 5, 20, 26, 22, 24, 25] experiments, a significant mobilization or redistribution of body fluids, and cardiovascular intolerance to passive tilt have been found. Experimentation has established also a relationship between orthostatic cardiovascular changes and diminished blood volume.[14, 15]

Of the three fluid compartments, the intravascular fluid compartment (blood volume) directly affects cardiovascular response to passive tilting. This effect is related not only to the total volume of blood present, but also to the availability of this blood for heart filling and delivery to the peripheral arterial system. The intravascular fluid compartment is of further importance in maintaining over-all fluid balance of the body. Fluids taken into the body are absorbed and generally pass into this compartment to be transported to other fluid compartments of the body. This compartment is intimately concerned with fluid and electrolyte control and elimination mechanisms.

This paper reports on observations of plasma volume and related measurements during two six hour water immersion experiments. Fluid and electrolyte observations are made. Consideration is given to the relation of changes in these measurements to the cardiovascular deconditioning seen in the specific experimental test situation of water immersion.

METHODS

Four healthy adult male college students in the age range 21 to 25 years who had participated previously in extensive bedrest studies were used as subjects. An additional subject who did not participate in the immersion studies was used as a control. Table I summarizes the subject characteristics.

TABLE I

SUBJECT CHARACTERISTICS

Subject Initial	Age (years)	Weight (kg.)	Height (cm.)	B. S. A. * (m^2)	Student Occupation
M. A. C.**	23	65.3	177.8	1.81	Student
C. E. R.	25	84.4	192.4	2.15	Student Athlete
R. S. H.	22	66.5	172.4	1.80	Student Athlete
W. F. M.	23	67.5	171.0	1.81	Dental Student
B. E. H.	21	70.2	177.8	1.88	Student

* From Dubois Body Surface Chart by Boothby and Sandiford

** Control Subject

The subjects underwent two periods of water immersion of six hours duration, preceded and followed by a tilt table test. During the periods of water immersion, the subjects were immersed in a head-out position. They were allowed a minimal amount of activity in the pool, but most of the time they remained in a sitting position. Accessory breathing apparatus was not used. The temperature of the water was maintained at approximately 93°F. Immersion test number one was followed the next day by immersion test number two.

During the immersion test number two, cuff-tourniquets were applied to the proximal part of all four extremities of the subjects. The cuffs were inflated simultaneously on all subjects by a single pressure bottle air source which provided a 60 millimeter mercury pressure referenced to the atmosphere. A one-minute-on, one-minute-off cycle was used with an inflate and deflate period of approximately five seconds duration. The cuffs on the lower extremities were located approximately 60-70 centimeters below the level of the water because of the posture the subjects maintained during immersion.

The subjects were immersed from 13:00 to 19:00 o'clock to correspond to a urine collection period that was used for a previous bedrest study on these subjects two months previously. During the periods of immersion, fluid intake and output were recorded carefully. Skin dry weights were obtained prior to and after immersion. The subjects were allowed to drink fluid ad libitum. They were fed after the tilt table test which immediately preceded the time of their entrance into the pool. This fluid intake was included as part of their over-all fluid intake. A malted milk was offered to them approximately four hours after start of immersion.

Venous blood was drawn immediately before and after water immersion for serum protein, sodium, potassium and osmolarity. Another blood sample was drawn after two hours of immersion for hemoglobin and hematocrit determinations. In addition to obtaining the urine volume for the total collection period, urine was collected over the six hour immersion period by periodic samples to monitor changes of specific gravity. Control data on urine volume and electrolyte excretion are available from the bedrest study completed earlier on these same subjects.

Plasma volumes by a radioisotope (IHSA) technique were determined immediately before and immediately after each immersion period. A pre-injection control sample of venous blood was collected for background radioactivity, after which one milliliter of the radioisotope solution then was injected. A dual radioisotope technique was utilized in order to provide some assessment of the transfer of albumin in and out of the vascular space during immersion and during the tilt tests that followed the immersion. For the first pre-immersion plasma volume determination, five microcuries of I^{125} were injected. After ten minutes mixing time, six milliliters of venous blood was withdrawn into a heparinized syringe. An additional sample was withdrawn two hours and six hours after the start of immersion to follow the disappearance rate of the tagged albumin. The blood collected was centrifuged and the plasma removed. Duplicate one milliliter aliquots of plasma were pipetted and counted in a scintillation well detector using a single channel analyzer for each determination. One microcurie of I^{131} was used in the post-immersion test of the first experiment. On the following day, the pre-immersion isotope dosage used was ten microcuries of I^{131} and the post-immersion dosage used was twenty microcuries of I^{125}. Plasma samples were obtained for counting after each of the tilt tests.

The disappearance of radioisotope tagged albumin from the vascular compartment was evaluated by counting the radioactivity of one milliliter of plasma collected after water immersion for the isotope injected prior to water immersion, to give a value of "albumin counts" per milliliter of plasma. Then, the plasma volume determined with a different isotope was multiplied by this value to obtain the tagged albumin in the circulating blood volume. The disappearance or exchange of a particular tagged albumin was obtained by comparisons to measurements made at the start of the immersion period.

Hematocrits were determined by the micro-capillary technique using the heparinized blood samples and spinning the capillary tubes for four minutes at 11,500 r.p.m. Hemoglobins were determined using an alkaline-buffer method to measure oxyhemoglobin. Serum and urine sodium and potassium were determined by a flame photometer. Serum protein was determined by the method of Kingsley[17]. Serum and urine osmolarity were determined immediately after collection of the samples using an "Advanced Osmometer". *

RESULTS

Table II. presents the plasma volume determinations made prior to and after each immersion period. A plasma volume was obtained on a control subject simultaneously with the test subjects except for the one time he was unavailable for testing at the conclusion of the first immersion period. The values are presented as milliliters of plasma volume per kilogram body weight. All four subjects showed a decline in plasma volume in the first six hour period of immersion, with a mean decrease of 12%. The plasma volumes had not returned to control values at the start of the second test the following day. However, during the second immersion period, to which cuffs were added, all subjects showed a small increase in plasma volume.

After the first period of water immersion, three of the four subjects (R. S. H., W. F. M., and B. E. H.) showed a marked drop in blood pressure resulting in syncope, and marked cardiac acceleration when they were tilted to the 70° head-up position. None of the subjects experienced syncope following the second period of immersion to which cuff-tourniquets were added during immersion, and blood pressure and heart rate changes were less marked. The response of these subjects to tilt tests performed before and after immersion is presented in detail in a separate report.[23]

* Advanced Instruments, Inc.; Newton Highlands, Massachusetts.

TABLE II

IHSA PLASMA VOLUMES (ml./kg.)

Subject	Test No. 1 Pre-Immersion	Test No. 1 Post-Immersion	Test No. 2 Pre-Immersion	Test No. 2 Post-Immersion
Control	54.9	----	53.0	54.1
C. E. R.	52.5	44.2	49.2	51.4
R. S. H.	45.9	44.7	44.7	49.4
W. F. M.	40.2	34.3	38.7	40.2
B. E. H.	47.1	40.3	44.3	46.6
Mean	46.4	40.9	44.2	46.9

Radioisotope tagged human serum albumin disappearance rates from the vascular system was observed in the subjects by the use of a dual radioisotope technique, and by progressively increasing the radioisotope test dosage. For the control subject who did not undergo water immersion tests, 19% of the tagged albumin disappeared from the circulating plasma after six hours on the first day, and 23% on the second experimental day. For the subjects undergoing the immersion tests, on day one the mean disappearance rate of tagged albumin was 35%, and on test day two (when no syncope was observed) it was 26%.

The changes in hematocrit, hemoglobin and serum protein during the study periods are indicated in Table III. During each test period, three of the four subjects showed a decreased hematocrit after two hours of immersion. The hematocrit at the end of the first immersion period had returned essentially to the value pre-immersion. These changes cannot be correlated directly with plasma volume or total blood volume changes. The hemoglobin concentrations showed random minor changes during the experiment. Serum protein concentration showed small irregular changes during both immersion periods.

Table IV presents the weight changes of the subjects, the fluid intake, and the urine output during each immersion period. Control values for each person are presented as the average urine volumes passed by these same subjects for a week control period prior to the study at which time the subjects were undergoing normal activities. The minimum and maximum urine volumes excreted for the six hour collection periods during this control week also are indicated. The urine volumes obtained during immersion are somewhat higher than the average control, but the range of volumes for the control days makes it difficult to describe a true water diuresis from this data, and the specific gravity of the urine did not change significantly during the experiments. The subjects did not complain of thirst. Urine sodium, potassium, and osmolarity for pooled six hour samples collected on each subject for the two immersion periods showed no significant or consistent change that differed from control data collected on these subjects previously.

Table V presents the serum sodium, potassium, and osmolarity measurements made before and after each period of immersion. There are no distinct trends of change or differences before and after immersion, except for the serum osmolarity of R. S. H., which changed from 295 mOs/kg. to 303 mOs/kg. during the second immersion period.

DISCUSSION

Our observation of an apparent hemodilution as shown by the hematocrit changes during the early phase of the water immersion periods, and a decrease in the plasma volume at the end of the six hour immersion period confirm the observations related to this measurement made by others.[9, 10, 11] Considerably more success was found in this experiment using radioisotope dilution techniques than was reported by McCally[18], and the consistency of response of the plasma

TABLE III

HEMATOCRIT, HEMOGLOBIN, SERUM PROTEIN

		Test No. 1			Test No. 2		
Subject	*	Hematocrit %	Hemoglobin gm-%	Protein gm-%	Hematocrit %	Hemoglobin gm-%	Protein gm-%
C. E. R.	Pre	43.5	12.7	7.4	44.5	11.9	7.6
	2 Hr	43.5	----	---	42.5	----	---
	Post	44.0	12.9	6.9	43.5	11.8	7.3
	P. Tilt	45.5	----	---	46.0	----	---
R. S. H.	Pre	48.0	14.0	6.8	48.0	13.0	6.8
	2 Hr	46.5	----	---	44.0	----	---
	Post	47.0	13.8	7.1	45.0	12.8	7.1
	P. Tilt	47.0	----	---	45.0	----	---
W. F. M.	Pre	48.0	12.5	8.1	47.0	12.2	7.9
	2 Hr	45.0	----	---	45.0	----	---
	Post	48.0	13.0	8.1	46.5	12.4	7.4
	P. Tilt	46.0	----	---	48.0	----	---
B. E. H.	Pre	44.0	12.3	7.2	44.5	11.8	7.0
	2 Hr	43.5	----	---	46.0	----	---
	Post	44.0	12.0	7.4	43.0	12.1	7.2
	P. Tilt	48.0	----	---	46.0	----	---

* Pre (Pre-Immersion)
Post (Post-Immersion)
P. Tilt (Post-Tilt)

TABLE IV

ORAL INTAKE - URINE OUTPUT DURING WATER IMMERSION

Subject	Control (ml.)*	Test No. 1 Intake (ml.)	Test No. 1 Output (ml.)	Test No. 1 Weight Change(kg.)	Test No. 2 Intake (ml.)	Test No. 2 Output (ml.)	Test No. 2 Weight Change(kg.)
C. E. R.	200 290 560	1200	900	-0.2	1160	530	+0.3
R. S. H.	220 295 385	800	510	-0.1	1500	190	+0.9
W. F. M.	270 500 770	800	390	-0.2	1300	360	+0.6
B. E. H.	195 412 770	1000	760	0.0	1500	620	+0.3

* One week control on each subject during normal activity, giving average urine volumes with minimum and maximum values for these periods above and below the average value.

TABLE V

SERUM MEASUREMENTS

Subject	Immersion	Test No. 1 Sodium meq/L	Test No. 1 Potassium meq/L	Test No. 1 Osmolarity mOs/kg.	Test No. 2 Sodium meq/L	Test No. 2 Potassium meq/L	Test No. 2 Osmolarity mOs/kg.
C. E. R.	Pre	151	4.8	294	146	4.1	300
	Post	151	4.4	299	151	4.1	297
R. S. H.	Pre	145	4.3	296	147	3.8	295
	Post	147	4.4	296	147	4.4	303
W. F. M.	Pre	147	5.1	296	145	4.9	296
	Post	152	4.4	297	148	4.7	297
B. E. H.	Pre	141	4.3	296	146	4.6	293
	Post	145	4.7	295	146	4.5	297

volume measurements on the control subject adds further support to this reliability. The plasma volume decrease may be related to the decreased tolerance to tilt noted in these subjects. However, it does not seem to be responsible for the entire spectrum of changes observed.

Green et al.[14] describe two dominant types of reactions to tilt after acute blood loss. When the blood loss does not exceed 14 milliliters per kilogram, Green reported that the response to tilt was characterized by a brisk cardiac acceleration with the usual systolic drop and the diastolic rise in blood pressure seen with tilting normal subjects. Cardioacceleration in the range of 20 beats per minute was found when 9-14 milliliters per kilogram was withdrawn. Occasionally they found a second type of tilt response characterized by marked tachycardia, air hunger, faintness, and a rapid fall in blood pressure to shock levels similar to the changes seen in the subjects in the water immersion experiment during which cuffs were not used. Green et al.[14] noted a progression from the first type of reaction to the second type in the subjects as blood was withdrawn progressively.

Our failure to observe a significant diuresis with water immersion is comparable to the findings observed by Benson et al.[2], but other investigators[9, 10, 1, 11, 12] have described a diuresis rather consistently. It is possible that a diuresis would have been observed in these subjects if they had been exposed to a longer period of immersion. Our data suggest that a significant and brisk diuretic response, with an associated intense thirst and change in body weight and possibly the vascular volume, no longer can be implicated as the initiating factors in the progression of events leading to the more severe tilt table intolerance seen after these water immersion experiments. Our failure to note a significant change in weight and in serum sodium, potassium, protein, and osmolarity, associated with definite plasma volume change suggests fluid-electrolyte-protein shifts out of the vascular compartment as one of the contributing causes of the intolerance to tilt after the first immersion period without cuffs.

Some estimate of the magnitude of the fluid and protein shift is available from the albumin disappearance study. Thirty-five percent of the circulating radioiodinated albumin disappeared during six hours of immersion. This was greater than the 19% seen in the control subject and the 26% of the test subjects following the immersion period to which cuffs were added. The disappearance rate of the control subject and the test subjects on the second day corresponds to the expected decay rate.[4, 16] Since there was no significant change in serum protein concentration associated with the disappearance of the radioactive albumin, the data suggest a shift from the circulating vascular space of an electrolyte-water-protein combination to the extravascular compartment.

The drop in plasma volumes seen in these studies (about 6 ml. per kg.) was associated with tilt responses of the type seen by Green with a much larger loss of blood and plasma. If response to tilting in the two situations can be compared, one must consider more complicated mechanisms responsible for the observations seen in this water immersion study. The increased disappearance rate of albumin from the vascular space suggests the possibility of erroneously high values for the plasma volume determined after immersion if there is a correspondingly more rapid loss of tagged albumin during the ten minute mixing period. A poor correlation of the hemoglobin and hematocrit changes with the IHSA plasma volume changes could result if the venous samples are not representative of the total circulating blood volume, especially in this acute experiment in which there appear to be alterations in the fluid-electrolyte-protein and plasma volume control mechanisms.

Any theory of the mechanisms involved in the tilt table intolerance also must consider the redistribution of the circulating blood volume seen in this study as well as pooling of blood due to loss of venomotor tone. Such changes could have resulted from the exposure to the relatively high water temperature. The protective action seen with the cuffs is still to be explained.

The preliminary observations presented here are presented to provoke new thoughts as to the possible physiological mechanisms for the condition called "cardiovascular deconditioning" seen with water immersion. An understanding of these changes can be learned only from further studies. Further, it is too early to imply that common mechanisms of action are responsible for the cardiovascular deconditioning of bedrest, chair rest, space flight, and water immersion.

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